Proof of concept review

Lapatinib: the evidence for its therapeutic value in metastatic breast cancer

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Abstract

Introduction: Breast cancer is the most common cancer affecting women. Many patients ultimately progress to metastatic disease and optimal management of this disease remains a significant therapeutic challenge. Lapatinib, a dual tyrosine kinase inhibitor, is in clinical development for treatment of this disease.

Aims: The objective of this article is to review the published evidence for the treatment of metastatic breast cancer with lapatinib, and assess its therapeutic potential.

Evidence review: Most evidence has appeared in meeting abstract reports of phase I and II studies in healthy volunteers and cancer patients. Four studies have included patients with exclusively breast cancer. Complete and partial responses and stable disease has been reported in some patients. Emerging evidence indicates that complete and partial responses can be achieved in some patients with metastatic breast cancer. Lapatinib appears to be well tolerated in cancer patients and the maximum tolerated dose is in the region of 1800 mg/day. In addition, it has been used in combination with other cancer treatments. Five ongoing or planned phase II monotherapy and three phase III combination-therapy studies with lapatinib have been identified.

Outcomes summary: The phase I and II studies reported to date have provided safety data and preliminary indications regarding efficacy. There is preliminary evidence that lapatinib can achieve objective response rates of 10–38% in patients with metastatic breast cancer. Patients with tumors overexpressing ErbB1 and/or ErbB2 are likely to benefit from lapatinib treatment.

Key words: lapatinib, GW572016, metastatic breast cancer, signal transduction, tyrosine kinase inhibition

Core evidence proof of concept summary for lapatinib in metastatic breast cancer

Outcome measure	Emerging evidence
Efficacy	Potential to use as monotherapy, or in combination, in patients with pretreated metastatic breast cancer
	Common dose for monotherapy is 1500 mg/day
Response rates	Some evidence that objective (complete or partial) responses may occur in 10–38% of patients
Biomarker expression	Partial responses seen in patients with tumors overexpressing ErbB2 (where measured)
Tolerability	Good tolerability with daily administration alone or in combination with paclitaxel or capecitabine
	Maximum tolerated dose is 1800 mg/day in cancer patients
	Once-daily dose regimen better tolerated than twice-daily regimen

Scope, aims, and objectives

Breast cancer is the most common cancer affecting women and is one of the leading causes of cancer death. A significant proportion of patients initially diagnosed with early-stage breast cancer ultimately progress to metastatic disease. Optimal management of metastatic breast cancer remains a significant therapeutic challenge.

Lapatinib (GSK572016) is a novel orally administered dual tyrosine kinase inhibitor in development for the treatment of solid tumors. It is currently being evaluated in phase II and phase III trials in patients with metastatic breast cancer.

The objective of this review is to evaluate the emerging evidence for the potential use of lapatinib in the treatment of metastatic breast cancer.

Methods

The English language medical literature was reviewed for relevant articles relating to lapatinib for the treatment of metastatic or advanced breast cancer. The following databases were searched on March 22, 2005 using the search terms "lapatinib OR GW572016" for articles published between January 1990 and March 2005 (inclusive):

- PubMed, www.ncbi.nlm.nih.gov/entrez
- Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluations Database (NHSEED), Health Technology Assessment (HTA), www.york.ac.uk/inst/crd/darehp.htm
- NHS HTA, www.ncchta.org
- National Guidelines Clearinghouse, www.guideline.gov
- National Institute for Health and Clinical Excellence (NICE), www.nice.org.uk
- Cochrane Database of Systematic Reviews, www.cochrane.org
- Clinical Evidence, www.clinicalevidence.com

In addition, the annual scientific sessions from the American Society of Clinical Oncology (ASCO), San Antonio Breast Cancer Symposium (SABCS), European Cancer Conference (ECCO), and European Society of Medical Oncology (ESMO) held between 2002 and 2005 were searched for relevant meeting abstracts. ClinicalTrials.gov was searched for information on ongoing phase II and III studies with lapatinib. A total of 22 articles were identified after animal, *in-vitro*, or other nonrelevant studies were excluded. One further article was identified after the search date and included in the evidence evaluation.

There have been a number of phase I and phase II studies conducted using lapatinib for the treatment of metastatic breast cancer. In addition, studies involving patients with a variety of solid tumors have been included here if results with breast cancer have been reported. Table 1 summarizes the levels of evidence of articles identified from the search strategy. No systematic reviews

Table 1	Evidence base included in the review		
	Number of records	
Category	**Full papers**	**Abstracts**
Initial search	9	32
records excluded	6	13
records included	3	19
Additional studies identified	1	0
Level 1 clinical evidence	0	0
Level 2 clinical evidence	1	0
Level ≥3 clinical evidence	3	10
trials other than RCT	0	9
case studies	0	0
Economic evidence	0	0

For definition of levels of evidence, see Editorial Information on inside back cover. RCT, randomized controlled trial.

were identified for the use of lapatinib. In addition, no economic publications have yet appeared.

Disease overview

Breast cancer is the most frequently diagnosed nonskin cancer in women. More than 41 000 new cases are diagnosed each year in the UK, accounting for about a third of all cancers in women. The lifetime risk for breast cancer in women is one in nine (Cancer Research UK 2004). During 2004 in the USA approximately 216 000 new cases of invasive breast cancer were predicted to occur in women and about 40 000 deaths were expected to result from the disease (ACS 2004). Only lung cancer causes more cancer-related deaths in women.

There are a number of risk factors associated with the development of breast cancer (reviewed in Veronesi et al. 2005). Age is the strongest risk factor associated with a diagnosis of the disease; breast cancer is rare in women under 30 years of age but the risk increases in older women. Other risk factors include a personal or family history of breast cancer, never having children or having the first child after 30 years of age, a long menstrual history (starting early and ending late in life), recent use of hormone replacement therapy or oral contraception, postmenopausal obesity, regular alcohol consumption, and mammographically dense breast tissue. In contrast, the risk is lowered by breastfeeding, moderate or vigorous physical activity, and maintenance of a healthy bodyweight.

Most patients presenting with breast cancer have disease localized to the breast and axillary lymph nodes and 40–50% of patients initially diagnosed with early breast cancer may develop metastatic disease. In addition, about 10% of patients with newly diagnosed breast cancer will have locally advanced and/or metastatic disease (Bernard-Marty et al. 2004). The most

common sites of metastatic disease are bone, liver, lungs, skin, and brain (Mincey & Perez 2004). Fortunately earlier detection and improved treatment have resulted in decreases in mortality rates of 2.3% per year from 1990 to 2000 (ACS 2004). Indeed, since 1990 declining mortality rates have been seen in western Europe and Australia as well as the Americas as a result of progress in these activities (Veronesi et al. 2005). Screening for breast cancer allows for the detection of cancers before they become palpable. Small tumors are more likely to be early-stage disease, have a better prognosis, and are more successfully treated (Tabar et al. 1999). Although earlier detection has contributed to a decline in rate, metastatic disease now represents the biggest clinical challenge in managing breast cancer. Despite progress in this area metastatic breast cancer remains essentially incurable and the median survival time is about 2 years after documentation of metastases (Bernard-Marty et al. 2004).

Current therapy options

Patient management following initial suspicion of breast cancer generally includes confirmation of the diagnosis, evaluation of stage of disease, and selection of therapy. Breast cancer is commonly treated by various combinations of surgery, radiation therapy, chemotherapy, and hormone therapy. Prognosis and selection of therapy may be influenced by the age and menopausal status of the patient, stage of the disease, histologic and nuclear grade of the primary tumor, measures of proliferative capacity, and status of various prognostic markers (Simpson et al. 2000).

The current treatment goals for the management of metastatic or advanced breast cancer are a delay in disease progression, prolongation of survival, amelioration of symptoms, and optimizing of quality of life (Veronesi et al. 2005). Several factors influence the decision regarding treatment choices for patients with metastatic cancer. These include the patient's overall condition (e.g. presence of comorbidities and their performance status), sites of metastases, previous treatment regimens, and biologic characteristics of the tumor. In addition, treatment of specific complications in specific organs is now used routinely. For example, bisphosphonates can be used to reduce bone pain and other skeletal events in women with advanced breast cancer (Veronesi et al. 2005).

When diagnosed with metastatic breast cancer it is critically important that the tumor should be tested (ideally from a new biopsy) for markers [particularly estrogen receptor (ER), progesterone receptor (PR) and ErbB2] against which therapies may be targeted (Mincey & Perez 2004).

Essentially there are three systemic treatment modalities for advanced breast cancer: endocrine therapy, chemotherapy, and biologic targeted therapy. Endocrine therapy is considered appropriate for patients with hormonally responsive tumors (positive for ER and/or PR) also involving soft tissues or bone and when the disease is not life threatening. If these criteria are not met then chemotherapy is the first choice (Mincey & Perez 2004).

Endocrine therapy has the benefit of combining efficacy and good quality of life outcomes with low toxicity (Bernard-Marty et al. 2004). Tamoxifen is recommended for premenopausal women with advanced disease although the luteinizing hormone-releasing hormone agonists are another therapeutic option. The first agents of choice for postmenopausal women are the aromatase inhibitors as they provide a therapeutic ratio superior to that of tamoxifen (Bernard-Marty et al. 2004). Endocrine therapy is mandatory in younger premenopausal patients with ER-positive tumors. However, treatment needs to be tailored in this population as most clinical experience has been gained in older premenopausal women (reviewed in Dellapasqua et al. 2005).

Chemotherapy is the only option for women with ER- and ErbB2-negative, endocrine-resistant disease. The most active drugs are the anthracyclines and taxanes followed by alkylating agents, antimetabolites, and vinca alkaloids. Docetaxel remains the reference agent in metastatic breast cancer (Hamilton & Hortobagyi 2005). Examples of single-agent response rates for some of these therapies include 35–50% for vinorelibine, 32–48% for docetaxel, 30–40% for doxorubicin and epirubicin, and 14–37% for gemcitabine (Hamilton & Hortobagyi 2005). However, complete responses are rare and disease progression is usually inevitable, and there is no consensus on the true impact of chemotherapy on survival and quality of life in patients with metastatic breast cancer (Bernard-Marty et al. 2004). No single chemotherapy regimen is best for all patients but with the variety of options available individualization of care is possible (Mincey & Perez 2004).

Biologic targeted therapy is based on molecules implicated in molecular pathways relevant to the biology of the breast cancer cell. The target should be measurable in the clinic, and its measurement should correlate with clinical outcome when the therapy is administered. It is vital that targeted therapy requires clinical validation, otherwise it is not targeted therapy (Sledge 2005). Targeted biologic therapies have the advantage of maximizing efficacy while often reducing toxicity compared with classical chemotherapeutic agents.

One target for biologic therapy is the ErbB family of receptors, which consists of four closely related members: ErbB1 (EGFR), ErbB2 (HER-2), ErbB3 (HER-3), and ErbB4 (HER-4). These receptors share the common structural features of an extracellular domain for ligand binding, a single transmembrane alfa-helix, and an intracellular domain containing regulatory sequences and tyrosine kinase regulator or receptor. Evidence suggests that ErbB2 acts mainly as a coreceptor, increasing the affinity of ligand binding to the dimeric receptor complex. Ligand binding induces dimerization of two identical (homodimer) or different (heterodimer) receptors. Signaling through ErbB2 and ErbB3 requires heterodimerization as ErbB2 has no known ligand and ErbB3 lacks tyrosine kinase activity (although it is a potent activator of this enzyme). Stimulation by a specific ligand confers a unique dimerization profile that is tumor- or tissue-specific (Olayioye et al. 2000).

Abnormal activation of ErbB receptor tyrosine kinase activity plays an important role in the development and subsequent progression of cancer. Tumors may have truncated or mutated receptors that confer constitutive activation of the receptor. Overexpression of ErbB2, triggering homodimeric activation of kinase activity, is seen in a significant proportion of breast (and ovarian) cancers where it is associated with poor prognosis (Olayioye et al. 2000). In addition, ErbB1 is also overexpressed in up to 30% of primary invasive breast cancers and is correlated with reduced overall survival, proliferation, and increased metastatic potential (Nicholson et al. 1990; Tsutsui et al. 2002).

At present trastuzumab, targeting ErbB2, is the one biologic agent approved for the treatment of metastatic breast cancer. The biologic significance of overexpression of ErbB2 in breast cancer, and the demonstration that monoclonal antibodies directed against ErbB2 inhibited malignant transformation in preclinical models, led to the development of trastuzumab. It is a humanized antibody composed of an antigen-binding component (from the murine monoclonal antibody 4D5) combined with human immunoglobulin G (IgG). Antibodies directed against ErbB2 affect tumor growth directly by altering the receptors' signaling properties and also indirectly by antibody-dependent cell-mediated toxicity and complement-dependent cytotoxicity (Sliwkowski et al. 1999).

Trastuzumab is one of the few agents that has led to an improvement of overall survival in metastatic breast cancer and so the evaluation of ErbB2 status has become crucial in deciding optimal treatment. Several issues surround the clinical use of trastuzumab, including methodology used to determine ErbB2 status, optimal administration regimen, risk of drug-related congestive heart failure, and emergence of resistance. About 60% of ErbB2 patients do not respond to trastuzumab, and in those who do respond, median duration of response to monotherapy has been reported to range from 3.7 to 8.4 months (Norum et al. 2005). Although randomized studies have not been conducted comparing single-agent trastuzumab with a combination of trastuzumab and chemotherapy, the combination is clearly superior to chemotherapy alone. In addition, preclinical synergy has been demonstrated with trastuzumab and several chemotherapeutic agents including carboplatin, cyclophosphamide, docetaxel, and vinorelibine (Hamilton & Hortobagyi 2005).

Cooperative activation of different ErbB family members through heterodimerization may evade the therapeutic efficacy of inhibition of a single receptor target which, for example, may in part explain the relatively low response rates with trastuzumab. Therefore, dual inhibition of both ErbB1 and ErbB2 appears an attractive therapeutic strategy. Lapatinib is a potent inhibitor of the tyrosine kinase activity of ErbB1 and ErbB2 in cells, ErbB-dependent tumor growth *in vitro*, and in animal models (Rusnak et al. 2001; Xia et al. 2002). This agent is in clinical development for the treatment of metastatic breast cancer. Studies for the treatment of other solid tumors expressing these markers are also ongoing.

The optimal management of metastatic breast cancer remains a significant therapeutic challenge. Single-agent therapy is frequently used for the management of asymptomatic patients with metastatic breast cancer. For patients with symptomatic or more extensive disease combination therapy is often used. No modern single agent offers a clear survival advantage over another, and other than ErbB2 and trastuzumab no molecular marker has been shown to consistently predict responses to any individual agent (Hamilton & Hortobagyi 2005). In the palliative setting both tolerability and quality of life issues are of critical importance. Because of unmet needs (improvements in quality of life, tolerability issues, and limited response rates) with existing treatments for metastatic breast cancer lapatinib is one of about 50 new agents currently being evaluated in clinical trials (Mincey & Perez 2004).

Outcomes achieved with lapatinib in clinical development

Several studies with lapatinib have included both efficacy and tolerability outcomes. Efficacy outcomes have been exclusively disease-orientated (response rates and biomarker expression). Lapatinib has been evaluated as monotherapy and also in combination with other therapeutic agents. Four studies have involved patients with exclusively breast cancer and several others have enrolled patients with a variety of solid tumors, including breast cancer.

Monotherapy

Preliminary evidence from a number of studies indicates objective responses (complete plus partial responses) to orally administered lapatinib 1500–1600 mg/day in about 10–38% of patients with metastatic breast cancer (Table 2).

Lapatinib 1500 mg/day is being studied in a phase II multicenter open-label trial in a population of 80 patients with metastatic breast cancer overexpressing ErbB2. Abstract reports of interim analysis showed that one complete response, three partial responses, and 15 instances of stable disease had been achieved in 41 patients recruited thus far (Blackwell et al. 2004a,b). A total of seven (17%) of these 41 patients remained progression-free at 6 months.

EGF10004 is a phase Ib, open-label study of lapatinib in heavily pretreated metastatic cancer patients with tumors accessible to biopsy. Outcomes measured in this study include clinical response at 8 weeks and expression of biomarkers (Dees et al. 2004; Burris et al. 2005; Spector et al. 2005). In this study, lapatinib 500–1600 mg/day was administered to 67 patients with a variety of metastatic carcinomas overexpressing ErbB1 and/or ErbB2. Four partial responses were observed, all in patients with paclitaxel- and trastuzumab-resistant metastatic breast cancer. Two of these responses occurred in women with recurrent inflammatory breast cancer. Disease stabilization (ranging from 8 to 41 weeks) was noted for 23 patients although the number with breast cancer was not stated. A subset of 33 patients in EGF10004 participated in an analysis of sequential biopsies.

Table 2 | Disease response and biomarker expression achieved with lapatinib in patients with metastatic breast cancer

Level of evidence	Outcomes	Drug and dosage	Study population	Reference
3[a]	Results from the first 41 patients included 1 CR, 3 PR, 15 SD (the clinical benefit rate, SD+PR, was 22% in the first 36 patients evaluated for efficacy) Total response for ≤8 weeks was 46.3% and 12 patients had ≤16 weeks progression-free survival	LAP (1500 mg/day)	56 patients with metastatic breast cancer overexpressing ErbB2 (enrolled by May 2004) (Study EGF20002)	Blackwell et al. 2004a Blackwell et al. 2004b
3	Four PR, all in patients with PAC- and TZM-resistant metastatic breast cancer 23 patients (with various carcinomas) had SD lasting 8–41 weeks Four PR occurred, all in breast cancer patents All patients with PR showed inhibition of the biomarkers p-ErbB1, cyclin D, and TGF-alfa SD occurred in 3 breast cancer patients Clinical responses occurred in patients who had not responded to TZM, indicating no crossresistance	LAP (500–1600 mg/day)	67 patients with a variety of metastatic carcinomas overexpressing ErbB1 and/or ErbB2 (Study EGF10004)	Burris et al. 2005 Dees et al. 2004 Burris et al. 2003a Burris 2004 Spector et al. 2003 Spector et al. 2004 Spector et al. 2005
3[a]	7 of 19 progression-free patients at 16 weeks achieved an OR (either CR or PR) Intact ErbB2 ECD and shorter duration of TZM therapy are likely predictors of response	LAP (1250–1500 mg/day)	81 patients with metastatic breast cancer progressing on TZM (Studies EGF20002 and EGF20008)	Blackwell et al. 2005
3[a]	PR in 5 patients, SD (≥8 weeks) in 6 patients, PD in 2 patients	LAP (1500 mg/day or 500 mg twice daily)	13 evaluable patients with ErbB2 expressing locally advanced or metastatic breast cancer	Gomez et al. 2005
3[a]	One patient with TZM-resistant breast cancer overexpressing ErbB2 had a PR with LAP 1600 mg/day; one further breast cancer patient had SD	LAP (900–1800 mg/day)	24 patients with advanced solid tumors	Minami et al. 2004
3[a]	One breast cancer patient treated with LAP 1600 mg/day had SD for 7 months	LAP (175–1800 mg/day, or 900 mg twice daily)	39 patients with various solid tumors (Study EGF10003)	Burris et al. 2003b Burris 2004
3[a]	Of 27 evaluable patients there was 1 CR, 5 PR, 10 SD, and 11 PD	LAP (750–1500 mg/day) plus TZM (standard regimen)	48 patients with ErbB2 overexpressing metastatic breast cancer	Storniolo et al. 2005
3[a]	Three OR in patients with taxane-resistant metastatic breast cancer One breast cancer patient had SD for ≥3 months	LAP (1250–1500 mg/day) plus PAC (135–225 mg/m^2)	26 patients with solid tumors (Study EGF10009)	Jones et al. 2003 Jones et al. 2004
3[a]	Within the 8 breast cancer patients there was 1 CR (inflammatory breast cancer refractory to TZM and chemotherapy) and 1 PR	LAP (1250–1500 mg/day) plus CAP (1500–2500 mg/m^2)	8 pretreated breast cancer patients (study included 45 patients in total with advanced solid tumors)	Schwartz et al. 2004 De Bono et al. 2003
3[a]	SD for >5 months in 4 patients (2 of whom had advanced breast cancer)	LAP (1250–1500 mg/day) plus LET (2.5 mg/day)	36 patients with solid tumors (EGF10030)	Chu et al. 2005

[a]Abstract.

CAP, capecitabine; CR, complete response; ECD, extracellular domain; LAP, lapatinib; LET, letrozole; OR, objective response; PAC, paclitaxel; PD, progressive disease; p-ErbB1, phospho-ErbB1; PR, partial response; SD, stable disease; TGF-alfa, transforming growth factor-alfa; TZM, trastuzumab.

Fourteen (42%) of these patients were women with metastatic breast cancer previously treated with multiple chemotherapeutic regimens, most in combination with trastuzumab and in some cases hormonal therapy. Biopsy analysis conducted on the tumors from the four patients with partial responses showed markedly elevated levels of activated phospho-ErbB2. In addition, inhibition of both cyclin D and transforming growth factor-alfa (TGF-alfa) (an ErbB1 ligand) was also seen in the biopsy samples.

Biomarker analysis has also been conducted on biopsy samples taken from two large phase II studies in metastatic breast cancer patients treated with lapatinib and trastuzumab-containing regimens (Blackwell et al. 2005). Early declines in the extracellular domain (ECD) of ErbB2 appear to predict a lapatinib response. Responders are likely to have an intact ErbB2 ECD and short duration of prior trastuzumab therapy.

Antitumor activity with lapatinib 900–1800 mg/day was reported in a meeting abstract of a phase I Japanese study in patients with advanced solid tumors (Minami et al. 2004). Of the two patients who had partial responses, one recipient of lapatinib 1600 mg/day had trastuzumab-resistant breast cancer overexpressing ErbB2 and negative for ER and PR expression. One further patient with breast cancer (and 11 other patients with various tumors) had stable disease. The authors recommended that phase II studies using lapatinib up to 1600 mg/day were warranted.

Lapatinib (1500 mg/day or 500 mg twice daily) has also shown promising activity as first-line treatment in patients with ErbB2-positive advanced or metastatic breast cancer (Gomez et al. 2005). Preliminary data from the first 13 patients demonstrated a partial response in five patients, stable disease (for at least 8 weeks) in six patients with the remaining two patients experiencing progressive disease. A total enrolment of 130 patients is planned for this study.

Most of the evidence with lapatinib is in patients overexpressing ErbB2. However, EGF10003 was a phase I study involving 39 patients with solid tumors independent of ErbB receptor status (Burris et al. 2003b). Nine patients with a variety of tumors had stable disease for up to 13 months. Only one of these patients had breast cancer and had stable disease for 7 months following treatment with lapatinib at 1600 mg/day (Burris 2004).

Combination therapy

Patients with metastatic breast cancer are already likely to be receiving systemic treatment, so the combination of lapatinib and other therapies is likely to reflect the situation in clinical practice. Results from a number of studies have shown the benefit of combining biologic therapy (trastuzumab) with endocrine therapy or chemotherapy for treating metastatic breast cancer (Bernard-Marty et al. 2004). To date four published studies have investigated lapatinib in combination with other treatments (Table 2).

Lapatinib combined with the standard weekly dosing of trastuzumab (4 mg/kg loading dose followed by weekly 2 mg/kg infusions) has shown promising clinical efficacy in pretreated patients with ErbB2 overexpressing metastatic breast cancer (Storniolo et al. 2005). Of 48 treated patients, 27 were evaluable for response in this phase I study. There was one complete response (duration 8 months), five partial responses (duration 2–7 months), 10 patients with stable disease (duration 1–5 months), and 11 patients with progressive disease.

In a study reported in a meeting abstract, among 45 patients with advanced solid tumors treated with lapatinib combined with capecitabine there were eight patients with pretreated breast cancer (De Bono et al. 2003; Schwartz et al. 2004). Within this subgroup there was one complete response in a patient with inflammatory breast cancer refractory to both trastuzumab and chemotherapy. This tumor overexpressed ErbB2 and had low levels of thymidlate synthase (a target for capecitabine). In addition, there was another patient with a partial response.

Lapatinib combined with paclitaxel was used in a study of 26 cancer patients. In this heterogeneous population there were three objective responses (i.e. complete or partial responses), all in patients with taxane-resistant metastatic cancer. One other breast cancer patient had stable disease for at least 3 months. The authors noted that a phase III study is planned comparing paclitaxel 155 mg/m^2 every 3 weeks with or without lapatinib 1500 mg/day in women with metastatic cancer (Jones et al. 2004).

Treatment with lapatinib plus letrozole led to four out of 36 patients with solid tumors experiencing stable disease for more than 5 months. Two of these patients had advanced breast cancer, but the proportion of all the evaluable patients with breast cancer was not stated (Chu et al. 2005).

Safety and tolerability

The safety and tolerability of lapatinib has been determined in both healthy volunteers and patients with cancer (Table 3). The maximum tolerated dose in cancer patients has been found to be 1800 mg/day. It has also been determined that single-daily dosing is better tolerated than twice-daily dosing.

Safety and pharmacokinetic data from single- and multiple-dose phase I trials of lapatinib in healthy volunteers have recently been published (Bence et al. 2005). The results showed that single doses of lapatinib (ranging from 10 to 250 mg) were well tolerated and there were no serious adverse events when compared with placebo. There were 23 adverse events recorded in a total of 47 administrations of lapatinib and all but one (a grade 2 headache after lapatinib 25 mg) were grade 1 (all adverse events were graded by the National Cancer Institute Common Toxicity Criteria version 2.0). Similarly, multiple doses of lapatinib were also well tolerated. The most common adverse event recorded in this study was gastrointestinal discomfort in the form of bloating, flatulence, and/or gas, occurring in five of 18 subjects receiving lapatinib. In addition, of the 28 adverse events recorded in subjects receiving either lapatinib or placebo, five were grade 2 and resolved without treatment; three volunteers receiving placebo had grade 2 bloating, flatulence and/or gas, and two subjects (one placebo and one lapatinib recipient) had a grade 2 elevation of liver function enzymes which resolved within a week.

EGF10003, a phase I maximum tolerated dose study, was the first involving administration of lapatinib to cancer patients (Burris et al. 2003b; Koch et al. 2003; Burris 2004). Preliminary tolerability results with lapatinib 175–1800 mg/day (given to 40 patients) and 900 mg twice daily (three patients) indicated no grade 3 toxicities with the daily doses but two cases of grade 3 diarrhea were reported for the twice-daily regimen (Burris 2004). A maximum tolerated dose study was also conducted in Japanese patients with advanced solid tumors (Minami et al. 2004). Groups of six patients were given one of four daily doses of lapatinib to determine the maximum tolerated dose, defined as the dose at which two of six patients had grade 3 toxicities. The maximum tolerated dose was found to be 1800 mg/day, the highest dose used in this phase I study. In addition, the tolerability of once-daily

Table 3 | Tolerability of lapatinib in healthy volunteers and patients with cancer

Level of evidence	Outcomes	Drug and dosage	Study population	Reference
2	No serious AEs seen in either study Single doses of ≤250 mg and multiple doses of ≤175 mg LAP were well tolerated in healthy subjects	Single-dose study LAP 10–250 mg or PLA Multiple-dose study LAP 25–175 mg/day or PLA	16 (single-dose study) and 27 (multiple-dose study) healthy volunteers	Bence et al. 2005
3[a]	Safety results from the first 41 patients showed prevalence of rash (37%), fatigue (34%) diarrhea (27%), nausea (24%), anorexia (15%), and vomiting (12%)	LAP (1500 mg/day)	56 patients with metastatic breast cancer overexpressing ErbB2 enrolled by May 2004 (EGF20002)	Blackwell et al. 2004a Blackwell et al. 2004b
3[a]	Maximum tolerated dose determined as 1800 mg/day	LAP (900–1800 mg/day)	24 patients with advanced solid tumors	Minami et al. 2004
3	Common AEs included transient grade 1 and 2 rash (12%) and diarrhea (30%) Five grade 3 drug-related toxicities (gastrointestinal and rash) occurred with four patients		67 patients with a variety of metastatic carcinomas overexpressing ErbB1 and/or ErbB2	Burris et al. 2005 Dees et al. 2004
3[a]	Grade 1–2 rash, diarrhea, nausea, vomiting, constipation, fatigue, and anorexia were the most frequent AEs following daily dosing. Grade 3 toxicity (diarrhea) only seen with twice-daily dosing Patients remaining on therapy for >4 months received LAP ≥1200 mg/day	LAP (175–1800 mg/day, or 900 mg twice daily)	39 cancer patients (Study EGF10003)	Koch et al. 2003 Burris et al. 2003b Burris 2004
3[a]	Most AEs were grade 1 (75% daily dose vs 71% twice daily). Diarrhea was the most frequent AE (17% daily dose vs 29% twice daily). Other AEs included fatigue (16%), nausea (16%), and rash (9%) with daily dosing; nausea (11%) and rash (11%) with twice-daily dosing 1 patient experienced grade 2 cardiac toxicity All daily doses were tolerated; 500 and 750 mg twice daily were better tolerated than 900 mg twice daily	LAP (175–1800 mg/day, or 500, 750, or 900 mg twice daily)	81 (64 in safety assessment) patients with advanced solid tumors	Pandite et al. 2004
3[a]	The optimally tolerated combination was found to be PAC 175 mg/m^2 (q3w) plus LAP 1500 mg/day Grade 4 neutropenia (n=5), grade 3 diarrhea (n=2), grade 3 neuropathy (n=1), and grade 3 arthralgia/myalgia (n=1) were reported No clear relationship between peak plasma concentrations and toxicity	LAP (1250–1500 mg/day) plus PAC (135–225 mg/m^2)	26 patients with solid tumors (Study EGF10009)	Jones et al. 2003 Jones et al. 2004
3[a]	Optimally tolerated combination was LAP 1250 mg/day with CAP 200 mg/m^2 q3w	LAP (1250–1500 mg/day), CAP (1500–2500 mg/m^2)	45 patients with advanced solid tumors	Schwartz et al. 2004 De Bono et al. 2003
3[a]	Optimally tolerated combination was LET 2.5 mg plus LAP 1500 mg/day	LAP (1250–1500 mg/day) plus LET (2.5 mg/day)	36 patients with solid tumors (Study EGF10030)	Chu et al. 2005

[a]Abstract.

AE, adverse event; CAP, capecitabine; LAP, lapatinib; LET, letrozole; PAC, paclitaxel; PLA, placebo; q3w, every 3 weeks.

doses of lapatinib 175–1800 mg was compared with 500, 750, or 900 mg twice daily in 64 patients with advanced solid tumors (Pandite et al. 2004). Most drug-related adverse events were reported to be grade 1 with diarrhea being the most frequent (17% once-daily vs 29% twice-daily dosing). Two patients receiving 900 mg twice daily had grade 3 diarrhea. It was concluded that lapatinib given once daily was well tolerated at all doses while 500 and 750 mg were better tolerated than 900 mg twice daily.

The incidence of adverse events was reported for 67 patients with metastatic carcinomas treated with daily doses of lapatinib 500–1600 mg (Dees et al. 2004; Burris et al. 2005). Five grade 3 drug-related toxicities (gastrointestinal and rash) were reported in four patients. The most frequent adverse events were transient grade 1 and 2 diarrhea (30%) and rash (12%). It was stated that there was no clear dose relationship for these adverse events, but that lapatinib was well tolerated.

Table 4	Ongoing or planned phase II and phase III studies with lapatinib for the treatment of metastatic breast cancer					
Study design	**Patients (n)**	**Endpoint**	**Inclusion criteria**	**Exclusion criteria**	**Reference**
Phase II					
LAP monotherapy NR, OL, UC, PA, T, MC, MN, 28-day study (Study EGF103009)	Unknown	Change in biomarkers from biopsies	Disease progression after anthracycline-containing regimen	Major surgery in preceding 2 weeks	Anon. 2005
LAP (1500 mg once daily and 500 mg twice daily) monotherapy R, OL, UC, PA, T, MC, MN, 28-day study (Study EGF20009)	Unknown	Efficacy and tolerability	Histologically confirmed invasive breast cancer with incurable IIIb or IIIc with T4 lesions	Any prior therapy	Anon. 2005
LAP (1500 mg/day) monotherapy T, OL, MC (Study EGF20002)	80	Response rate Tumor tissue and serum biomarker expression	Trastuzumab-refractory metastatic breast cancer overexpressing ErbB2	Not known	Blackwell et al. 2004a
LAP (1500 mg/day) monotherapy T, OL, MC	160	Safety and efficacy in ErbB2-positive and ErbB2-negative groups	Metastatic breast cancer	Not known	Burstein et al. 2004
LAP T, MC (Study CDR0000398179)	Unknown	CNS response rate assessed by MRI	ErbB2 overexpressing invasive breast cancer with CNS metastases	No concurrent anticancer biologic or immunotherapy	Anon. 2005
Phase III					
CAP ± LAP R, OL, AC, PA, T (Study 100151)	Unknown	Safety and efficacy	Metastatic breast cancer overexpressing ErbB2	Severe cardiac disease	Anon. 2005
LET ± LAP T, R, DB, PC, PA, MC, MN (Study EGF30008)	Unknown	Efficacy and tolerability	Stage IIIb, IIIc with T4 lesion, or IV breast cancer	Prior therapy for advanced or metastatic breast cancer	Anon. 2005
PAC ± LAP T, R, DB, PC, PA, MC, MN (Study EGF30001)	Unknown	Efficacy and safety	Tumor tissue available for testing	Prior therapy for advanced or metastatic breast cancer	Anon. 2005

AC, active control; CAP, capecitabine; CNS, central nervous system; DB, double blind; LAP, lapatinib; LET, letrozole; MC, multicenter; MN, multinational; MRI, magnetic resonance imaging; NR, nonrandomized; OL, open label; PA, parallel assignment; PAC, paclitaxel; PC, placebo controlled; PLA, placebo; R, randomized; T, treatment; UC, uncontrolled.

In the ongoing study EGF20002, lapatinib 1500 mg/day is being used to treat women with trastuzumab-refractory metastatic breast cancer (Blackwell et al. 2004a,b). For 41 patients with preliminary safety data there were 14 with grade 3–4 events including grade 3 rash (n=1), grade 3 fatigue (n=2), and grade 3 diarrhea (n=4). Lapatinib appeared to be well tolerated in this population.

Optimally tolerated doses of lapatinib when used in combination with other treatments have also been determined in phase I studies with cancer patients. The combination of paclitaxel and lapatinib was studied at six dose levels in 26 patients (Jones et al. 2003, 2004). Due to the cumulative neuropathy, and dose-limiting diarrhea with multiple paclitaxel doses ≥200 mg/m^2, the optimally tolerated regimen was paclitaxel 175 mg/m^2 every 3 weeks plus lapatinib 1500 mg/day. In addition, a dose-escalation study was carried out with lapatinib plus capecitabine (De Bono et al. 2003; Schwartz et al. 2004). Cancer patients (n=24) received 14 days' treatment with capecitabine (1500–2500 mg/m^2) and lapatinib 1250–1500 mg/day every 3 weeks. Dose-limiting toxicities including mucositis, anorexia, rash, diarrhea, fatigue, and bleeding stomatitis, resulted in an optimally tolerated regimen of lapatinib 1250 mg plus capecitabine 2000 mg/m^2. In agreement with previous studies (Dees et al. 2004) it was reported that no clear relationship exists between peak plasma concentrations and toxicity. Grade 1–2 diarrhea, nausea, rash, and fatigue were the common nonhematologic toxicities experienced in cancer patients (n=36) treated with the optimally tolerated regimen of lapatinib (1500 mg/day) plus letrozole (2.5 mg/day) (Chu et al. 2005).

Clinical development

Ongoing and future phase II and III studies with lapatinib for the treatment of metastatic breast cancer are shown in Table 4. There are five phase II studies all using lapatinib monotherapy. One trial will investigate the safety and efficacy of lapatinib in 160 patients with ErbB2 expressing and nonexpressing tumors.

There are three phase III randomized studies planned in patients with metastatic breast cancer. All these studies involve capecitabine, letrozole, or paclitaxel alone compared with the respective combination with lapatinib. Two studies are double blind and placebo-controlled while the third (capecitabine plus lapatinib) is open label.

Outcomes from all these future studies will be crucial in confirming the potential benefit of lapatinib for the treatment of metastatic breast cancer.

Resource utilization

At present optimal treatment of metastatic breast cancer remains a significant therapeutic challenge. Many patients will have been treated with other regimens and resistance to some of these therapies may have developed, limiting the choice of other therapeutic options. A treatment which can affect nonresistant targets with good tolerability and improved disease- and patient-orientated outcomes would have significant impact on disease management for metastatic breast cancer.

With pressure increasing on all healthcare budgets significant resources may need to be allocated to finance new therapies. When considering metastatic breast cancer there is competition for these resources from allocation to prevention, primary therapy or palliative care. Therefore it is important to determine effects on health with costs of new treatment. Recently an analysis of the cost effectiveness of trastuzumab has been conducted as this agent has imposed a significant burden on healthcare budgets worldwide (Norum et al. 2005). Results from this analysis showed that the drug was associated with between 0.3 and 0.7 life years gained at a median cost per patient of €44 196, yielding costs per life year saved in the range of €63 137–162 417 depending on survival benefit and discount rate employed. Clearly the costs per life year gained are very high and many healthcare systems will have difficulty in accepting this high cost regimen as standard (Norum et al. 2005). Factors that may change this conclusion include reductions in the cost of the drug, altering the dosing regimen, and improvements in survival data. Therefore, the generation of favorable pharmacoeconomic data is vitally important for any new treatment in this therapy area.

Patient group/population

Lapatinib is designed to interact with both ErbB2 and ErbB1. Patients overexpressing these markers on tumors are most likely to demonstrate greatest benefit from treatment with lapatinib. Therefore, the ability to biopsy the tumor and confirmation of the presence of these markers is an important step. However, it is interesting to note that some patients lacking tumor marker expression can respond to targeted therapy. Cetuximab targets ErbB1 and is active in metastatic colorectal cancer, yet it has been reported recently that colorectal cancer patients with ErbB1-negative tumors also have the potential to respond to cetuximab therapy (Chung et al. 2005). One reason for this is that analysis of ErbB1 by current immunohistochemical techniques does not appear to have predictive value and so exclusion of patients from treatment based on their apparent ErbB1 tumor status may not be warranted (Chung et al. 2005). Therefore, whether patients with metastatic breast cancer with ErbB2 and/or ErbB1 negative tumors (both determined by immunohistochemistry) respond to lapatinib remains to be determined.

To date, the patient populations in which lapatinib has been evaluated have included groups that have tumors overexpressing ErbB2 and/or ErbB1 or have been heavily pretreated with other therapeutic agents. Using lapatinib in patients with metastatic breast cancer in the phase I and phase II studies has resulted in positive disease-orientated outcomes including response rates, disease progression, and biomarkers.

It is likely that lapatinib will be evaluated initially in larger studies involving these patient populations as they would be expected to benefit most from this targeted therapy. Involving larger populations may give the opportunity to determine patient-oriented outcomes including quality of life measures.

Clinical potential

A number of meeting abstracts of completed and ongoing studies have provided preliminary evidence of the achievement of objective responses (range 10–38%) and stable disease in patients with advanced or metastatic breast cancer. There have also been reports of the effect of lapatinib on expression of tumor markers from biopsies. In a preliminary study, partial responses with lapatinib all occurred in patients with ErbB2-expressing breast cancers. In addition, lapatinib inhibited expression of cyclin D and TGF-alfa expression in tumors from these patients (Spector et al. 2005).

Lapatinib appears to be well tolerated in cancer patients and the maximum tolerated dose is in the region of 1800 mg/day. Optimal doses of lapatinib have been lower than this when used in combination with other agents (e.g. trastuzumab, letrozole, paclitaxel, or capecitabine). The most frequent adverse events reported with lapatinib have been rash and diarrhea typically of grade 1 or 2, but cases of grade 3 or 4 have been reported.

Health-related quality of life outcomes may be a measure that can be explored if other outcomes with lapatinib show promise. Over the past 10 years many new promising agents have been introduced and have led to studies in which survival benefits have been sought for metastatic breast cancer. The metastatic setting has given rise to the largest single group of quality of life trials in breast cancer. Unfortunately, health-related quality of life outcomes in these studies have generally provided little additional

information beyond that obtained from traditional medical outcomes, including toxicity (Goodwin et al. 2003). Therefore, any new treatment for metastatic breast cancer that shows benefits in quality of life outcomes is likely to be an advantage compared with existing therapy.

Preliminary evidence suggests that the best results with lapatinib will be gained in patients overexpressing the target markers ErbB2 and/or ErbB1. Thus it will be possible to target these patients most likely to benefit from treatment. At present metastatic breast cancer is associated with a poor prognosis, so reports that lapatinib (as monotherapy or in combination with other agents) has achieved complete and partial responses in some patients is encouraging and suggests that it could have an impact in treating this disease.

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