SPECIAL ARTICLE

Lapatinib: clinical benefit in patients with HER2-positive advanced breast cancer

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ABSTRACT

Background: Lapatinib, a tyrosine kinase inhibitor of human epidermal growth factor receptor 2 (HER2), has shown activity in combination with capecitabine in patients with HER2-positive advanced breast cancer progressive on standard treatment regimens. We present results on preapproval drug access for this combination in such patients occurring in the general oncology practice in the Netherlands.

Methods: Patients with HER2-positive advanced breast cancer progressive on schedules containing anthracyclines, taxanes, and trastuzumab were eligible. Brain metastases were allowed if stable. Lapatinib 1250 mg/day was given continuously in combination with capecitabine 1000 mg/m² twice daily for two weeks in a three-week cycle. Efficacy was assessed by use of response evaluation criteria in solid tumours version 1.0. Progression-free survival (PFS) and overall survival (OS) were calculated.

Results: Eighty-three patients were enrolled from January 2007 until July 2008. The combination was generally well tolerated and the most common drug-related serious adverse events were nausea and/or vomiting (5%) and diarrhoea (2%). Seventy-eight patients were evaluable for response. Clinical benefit (response or stable disease for at least 12 weeks) was observed in 50 patients (64%) of whom 15 had a partial response and 35 stable disease. The median PFS and OS were 17 weeks (95% CI: 13 to 21) and 39 weeks (95% CI: 24 to 54), respectively. For OS, higher Eastern Cooperative Oncology Group (ECOG) status (p=0.016), brain metastases at study entry (p=0.010) and higher number of metastatic sites (p=0.012) were significantly negative predictive factors.

Conclusion: In a patient population with heavily pretreated HER2-positive advanced breast cancer lapatinib plus capecitabine was well tolerated and offered clinical benefit.

KEYWORDS

Advanced breast cancer, capecitabine, HER2, lapatinib

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2; ErbB2) is overexpressed in 20% of patients with breast cancer. HER2 amplification is associated with a more aggressive phenotype.[1,2] Trastuzumab is a humanised monoclonal antibody against the extracellular domain of HER2. Combination with chemotherapy improves overall survival in patients with HER2-positive breast cancer, both in the metastatic and in the adjuvant setting.[3] Recently, lapatinib, an oral small molecule tyrosine kinase inhibitor targeting both HER2 and epidermal growth factor receptor (EGFR; HER1), has been approved for patients with advanced HER2-positive breast cancer previously treated with other anticancer drugs including trastuzumab. It is licensed for use in these patients in combination with capecitabine.[4,5] Several trials have demonstrated the safety and efficacy of lapatinib alone and in combination with capecitabine, paclitaxel or endocrine therapy in patients with advanced HER2-positive breast cancer.[4-9] Lapatinib is not active against EGFR-positive/HER2-negative disease.[8,10] Of

interest, lapatinib can cross the blood-brain barrier and has modest activity in breast cancer metastases in the central nervous system.[4,7,8,10,11] As monotherapy, lapatinib is well tolerated. Main toxicities are mild diarrhoea, nausea and skin rash.[12] Cardiac toxicity is rarely seen with lapatinib.[13]
In the registration trial in which the lapatinib + capecitabine combination was investigated in HER2-positive breast cancer patients who had previously been treated with an anthracycline, a taxane, and trastuzumab, disease progression was significantly delayed.[4,5] Median time-to-progression with the combination was 6.2 months as compared with 4.3 months for treatment with capecitabine alone (p=0.00013). This improvement was achieved without an increase in serious toxic effects or symptomatic cardiac events. A global Lapatinib Expanded Access Program was initiated in 2007 to offer preapproval drug access to lapatinib in combination with capecitabine in order to provide potential clinical benefit to patients with HER2-positive breast cancer, who had previously received anthracyclines, taxanes and trastuzumab. In contrast to the strict inclusion and exclusion criteria in the registration trial, the program allowed entry of a broader patient population: eligibility criteria allowed nonmeasurable disease, Eastern Cooperative Oncology Group (ECOG) performance status 2, previous capecitabine treatment, irradiated brain metastases if stable, and a maximum dose of dexamethasone 2 mg/day.

METHODS

Patients

Eligible patients had HER2-positive locally advanced or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab. Previous treatment with capecitabine was permitted. Patients had measurable or evaluable disease; an ECOG performance status of 0 to 2; a left ventricular ejection fraction (LVEF) within the institution's normal range; a life expectancy of at least 12 weeks; adequate renal, hepatic, and haematological function: haemoglobin ≥9 g/dl, neutrophils ≥1.5 x 10^9/l, platelets ≥100 x 10^9/l, serum bilirubin ≤3 x upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase ≤5 x ULN, calculated creatinine clearance according to the Cockcroft and Gault method ≥30 ml/min. Patients with central nervous system (CNS) metastases were eligible if they had been clinically stable for at least three months; a dexamethasone dose >2 mg/day and anticonvulsant therapy were not allowed. Since lapatinib is predominantly metabolised by the cytochrome P450 isoenzyme 3A4 (CYP3A4), inhibitors or inducers of CYP3A4 were prohibited.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The institutional review board of each participating institution approved the study protocol. All patients gave written informed consent.

Treatment

Treatment consisted of lapatinib 1250 mg/day continuously, one hour before or after breakfast and capecitabine 1000 mg/m^2 twice daily for two weeks in a three-week cycle. In case of side effects, standard recommendations for lapatinib and capecitabine dose modifications were advised according to the protocol. Briefly, lapatinib was withheld for up to 14 days for grade 2 haematological toxicity or any grade 3 or 4 toxicity. After recovery to grade 0 or 1, lapatinib was to be resumed at a dose of 1250 mg/day, although the site investigators could reduce the dose to 1000 mg/day if this was considered to be in the patient's interest. Resumption of lapatinib administration after grade 4 toxicity was optional, but required a dose reduction to 1000 mg/day. Lapatinib was permanently discontinued if improvement (a change to grade 0 or 1) did not occur within 14 days or if grade 3 or 4 interstitial pneumonitis or cardiac dysfunction occurred. Treatment continued until the investigator identified disease progression or unacceptable toxic effects.

Measurements

Patients were clinically assessed every three weeks and at the end of treatment. Side effects were recorded as serious adverse events (SAEs), defined as any event that was fatal, life-threatening, disabling or incapacitating or resulted in hospitalisation, prolonged a hospital stay and any experience which the investigator regarded as serious or which would suggest any significant hazard, contraindication, side effect or precaution that might be associated with the use of the drug. Monitoring of the LVEF by means of echocardiography or multiple gated acquisition scanning was performed every 12 weeks with the use of the same technique for the duration of the study. A cardiac event was defined as a decline in the LVEF that was symptomatic or was asymptomatic, but with a relative decrease of 20% or more from baseline or to a level below the institution's normal range.
Efficacy was assessed every 12 weeks according to the response evaluation criteria in solid tumours (RECIST) version 1.0. Progression-free survival (PFS) was defined as the time from the start of treatment until disease progressed or death from any cause. Overall survival (OS) was defined as the time from the start of treatment until death from any cause. Clinical benefit was defined as a complete response, partial response or stable disease for at least 12 weeks.

Statistics

Comparison of categorical data between groups was done using the χ^2 test or Fisher's exact test. PFS and OS

were assessed using Kaplan-Meier curves. Comparison of survival between groups was done with the log-rank test or the log-rank test for trend in case of ordered groups (ECOG status and number of metastatic sites). Multivariate analysis of prognostic factors (ECOG status, prior treatment, disease extent) was done using Cox regression. P values (two-sided) ≤0.05 were considered significant.

RESULTS

Patients and treatment duration

Eighty-three patients were enrolled in the expanded access study in the Netherlands from January 2007 until July 2008. Patient characteristics are shown in *table 1*. The median age was 50 years and the median ECOG performance score was 1. At the start of treatment, 98% of patients had metastatic disease and 53% had a median of three different sites. Thirty patients (36%) had central nervous system (CNS) metastases. Prior treatment consisted of a median of one hormonal (range: 0 to 5) and three cytotoxic schedules (range: 1 to 8) and 56 patients (67%) had received a prior fluoropyrimidine.

Table 1. *Baseline patient characteristics*

Characteristics	Numbers of patients or median (range)	%
Age (years)		
• Median	50	
• Range	26-70	
ECOG performance status		
• 0	18	22
• 1	50	60
• 2	15	18
Hormone receptor status		
• Positive for ER and/or PR	42	51
• Negative	40	48
• Unknown	1	1
Stage of disease		
• Locally advanced	2	2
• Metastatic	81	98
No. of metastatic sites		
• >3	44	53
• 2	28	34
• 1	11	13
Metastatic sites		
• Bone	52	63
• Lung	36	43
• Liver	53	64
• Brain	30	36
• Lymph node	38	46
• (Sub)cutaneous	17	20
• Other	12	14
Previous chemotherapy regimens (incl. adjuvant)		
• Median	3	
• Range	1-8	
Previous fluoropyrimidine	56	67

ER = oestrogen receptor; PR = progesterone receptor; No = number.

The median treatment duration of lapatinib plus capecitabine was 18 weeks (range 3.5 to 68 weeks). Seventy-eight patients discontinued treatment, most frequently because of progressive disease, and entered into the follow-up phase. Additional discontinuation reasons were toxicity (4%) and withdrawal of consent (1%).

Safety

All patients were evaluable for safety analysis. SAEs were reported in 19 patients of whom seven were considered to be related to the study drug. These SAEs consisted of nausea and/or vomiting (4 reports), diarrhoea (2), dehydration (1), increase in hepatic enzymes (1), malaise (1) and venous thrombosis (1). In four patients fatal SAEs were reported: myocardial ischaemia, cardiogenic shock, central nervous system metastases and arterial haemorrhage, respectively. These four events were not considered to be related to treatment in the opinion of the reporting investigator. The safety profile of lapatinib plus capecitabine was consistent with other studies on this combination.[4] Toxicity resulted in withdrawal from study drug in 4% of patients.

Efficacy and determinants for survival

The efficacy endpoints are depicted in *table 2* and *figures 1A* and *B*. The median PFS in all evaluable patients was 17 weeks (95% CI: 13 to 21; *figure 1A*). OS for all patients at a median follow-up of 35 weeks was 39 weeks (95% CI: 24 to 54; *figure 1B*). Seventy-eight patients were evaluable for response. A partial response was observed in 15 patients (three not confirmed) resulting in an overall response rate of 19% (95% CI: 11 to 30). Stable disease for at least 12 weeks occurred in 35 patients (45%). Therefore, the clinical benefit rate was 64%. *Figure 2* illustrates a partial response in a single patient upon treatment with the lapatinib + capecitabine combination.

Several patient characteristics were tested for a possible relation with OS. OS decreased significantly with increasing ECOG status (p=0.016; *figure 3A*). Additionally, survival decreased with a higher number of metastatic sites: median survival gradually shortened from 64 weeks if one site was reported to 29 weeks if five or more sites were present (p=0.012). The number of prior hormonal

Table 2. *Efficacy in evaluable patients (n=78)*

Endpoint	Numbers of patients	%
Complete response (CR)	0	0
Partial response (PR)	15	19
Stable disease (SD)	35	45
Progressive disease (PD)	28	36
Clinical benefit (PR + SD ≥12 weeks)	50	64

Figure 1. *Kaplan-Meier curves of progression-free survival (A) and overall survival (B) of patients with HER2-positive advanced breast cancer treated with lapatinib and capecitabine*

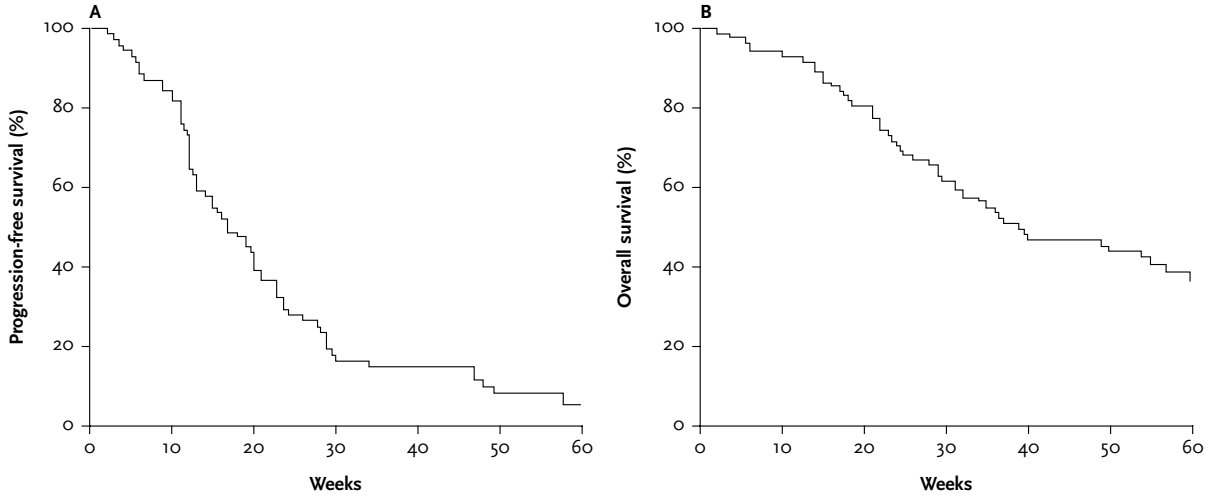


Figure 2. *Liver metastasis before (A) and after (B) treatment with lapatinib and capecitabine*

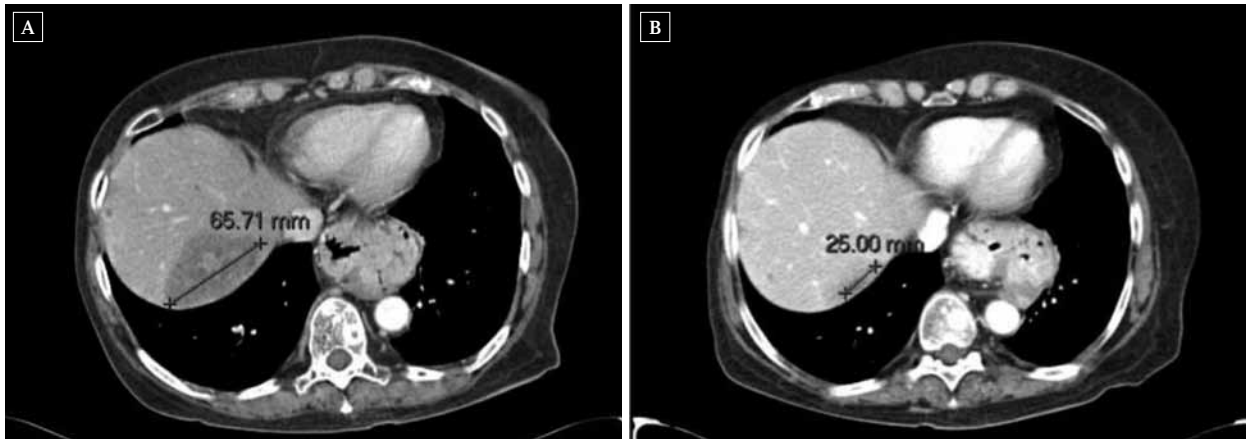
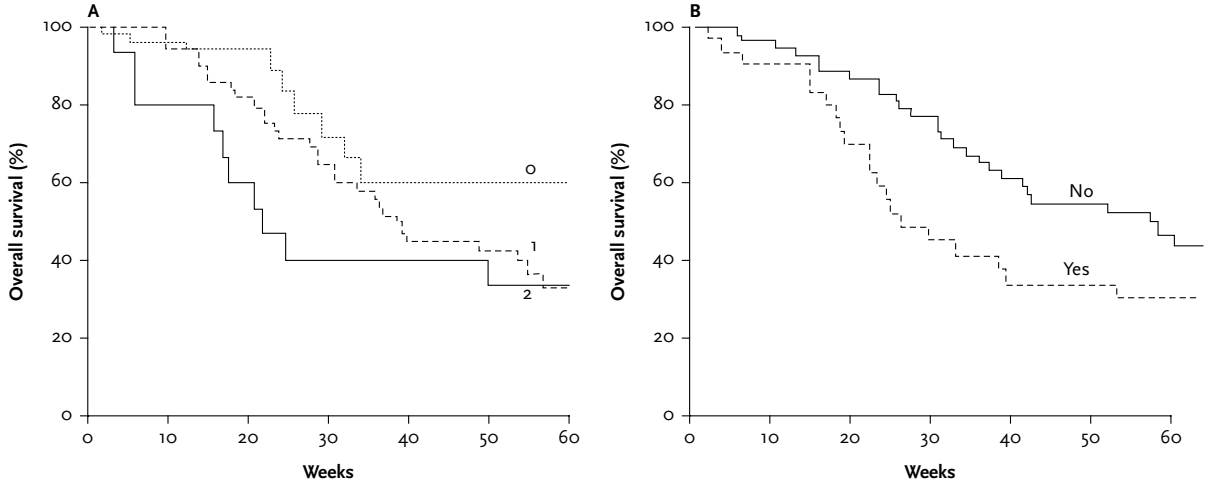


Figure 3. *Overall survival in relation to Eastern Cooperative Oncology Group status (p=0.016) (A) and the presence (yes) or absence (no) of brain metastases at study entry (p=0.010) (B) of patients with HER2-positive advanced breast cancer treated with lapatinib and capecitabine*



and chemotherapy schedules was not significantly related to outcome. The median OS of 35 weeks in patients with prior fluoropyrimidine exposure, either consisting of a 5-fluorouracil-containing regimen or capecitabine, tended to be shorter when compared with the 55 weeks (p=0.143) in patients without previous fluoropyrimidine treatment. The presence of brain metastases at entry into the study was predictive of a worse survival (p=0.010; *figure 3B*).

DISCUSSION

The combination of lapatinib and capecitabine was well tolerated and provided clinical benefit in a population of patients with heavily pretreated HER2-positive advanced breast cancer. Inclusion criteria were less strict than in the registration trial. Therefore, our results represent the safety profile and efficacy that can be expected in a patient population known to occur in the general oncology practice.

Although slightly different study designs do not permit comparison of data, in our patients treated with lapatinib and capecitabine the median OS was nine months, whereas this was 15.6 months in the registration trial.[5] Differences in baseline inclusion criteria, such as performance status, might explain this finding as ECOG status was significantly related to OS. Brain metastases at study entry and a higher number of metastatic sites were also found to be related to a worse OS. Data of the recently published global Lapatinib Expanded Access Program showed a median PFS of 21.1 weeks and a median OS of nine months,[14] which are in line with the results of a similar program from the United Kingdom[15] and the current study. The majority of our patients responded or had stable disease for at least 12 weeks (maximal 68 weeks), which may be considered as clinical benefit. We, therefore, believe that the lapatinib + capecitabine schedule is a useful addition to the treatment armamentarium for patients with HER-2-positive advanced breast cancer. The current study showed a trend towards a better survival for patients who had not received previous fluoropyrimidine treatment, which reflected the results observed in the global lapatinib program.[14] It might be considered to reserve capecitabine for its combination with lapatinib in patients with HER2-positive disease. Further characterisation of the predictors for response is important to select patients who might particularly benefit from this combination.

The limitation of our study is that it concerns an expanded access program and data were partially analysed in a retrospective way. Besides SAEs, common adverse events were not required to be reported. For toxicities known to occur from the lapatinib + capecitabine combination, such as diarrhoea, nausea, vomiting, hand-foot syndrome, and skin rash,[4] the protocol was followed for dose delays or reductions depending on the severity of adverse events. We observed that the drug-related SAEs were consistent with the global lapatinib program and they generally resolved upon treatment discontinuation. In this study no drug-related cardiac SAEs were reported, which is in agreement with the favourable cardiac toxicity profile of lapatinib.[13] These safety data also support the lapatinib + capecitabine combination as an appropriate new treatment option for heavily pretreated patients with HER2-positive disease.

Brain metastases develop in 25 to 40% of patients with advanced HER2-positive breast cancer,[16] which is in accordance with the 36% of the patients included in this study. Although the presence of brain metastases at entry into the study was predictive of a worse survival, the PFS of patients with evaluable brain metastases (n=22) was not different from the overall PFS (data not shown). There are limited therapeutic options for these patients after cranial radiotherapy. In a phase II trial, CNS objective responses obtained with lapatinib monotherapy as well as with the lapatinib + capecitabine schedule were observed in 6 and 20% of patients, respectively.[17] An exploratory analysis revealed a ≥20% volumetric reduction of CNS lesions in 21 and 40% of patients, respectively. Prospective trials of lapatinib combinations are underway in patients with CNS metastases.

The observed clinical benefit of the lapatinib + capecitabine treatment might be explained by different features of lapatinib to escape the mechanisms of resistance to earlier treatments. First, patients with advanced breast cancer expressing p95HER2, a constitutively active, truncated form of HER2 with kinase activity but lacking the extracellular domain, have a low chance of a response to trastuzumab.[18] Lapatinib, as an intracellular small molecule, has been shown to inhibit p95HER2 phosphorylation *in vitro*, leading to reduced downstream phosphorylation of Akt and MAPK, and inhibition of cell growth as well as experimental tumour growth. Second, HER2 epitope masking may also be a mechanism of resistance to trastuzumab. Mucin 4 is a large, highly *O*-glycosylated membrane-associated glycoprotein that hinders the binding of an antibody, but a tyrosine kinase inhibitor may reach its target.[19] Possible advantages of lapatinib over resistance to other HER2 inhibitors should be further unravelled. This also holds for the role of lapatinib in the adjuvant setting. In current clinical trials in early HER2-positive breast cancer lapatinib is being compared with trastuzumab, with trastuzumab followed by lapatinib, or with a combination of lapatinib and trastuzumab (ALTTO) or lapatinib is being compared with control in a delayed adjuvant therapy design (TEACH).

In conclusion, exploratory data from lapatinib in combination with capecitabine from eight Dutch hospitals confirmed that this schedule is well tolerated. The combination provides clinical benefit in the majority of heavily pretreated patients with HER2-positive metastatic breast cancer, including

patients who have been treated with a fluoropyrimidine before and patients with brain metastases.

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