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Combination Therapy of Lapatinib and Capecitabine for ErbB2-Positive Metastatic or Locally Advanced Breast Cancer: Results from the Lapatinib Expanded Access Program (LEAP) in Central and Eastern Europe

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Keywords

Lapatinib · ErbB2 · HER-2 · Breast cancer · Cardiac safety · Left ventricular ejection fraction

Schlüsselwörter

Lapatinib · ErbB2 · HER-2 · Mammakarzinom · Kardiale Toxizität · Linksventrikuläre Auswurffraktion

Summary

Background: The Lapatinib Expanded Access Program (LEAP) was initiated in 45 countries to provide lapatinib in combination with capecitabine to patients with ErbB2 (HER-2)-positive breast cancer already treated with anthracyclines, taxanes and trastuzumab. We report the results from 12 Central and Eastern European countries. **Patients and Methods:** By 30 September 2008, 293 patients were enrolled. Patients were monitored for serious adverse events (SAEs) and for any decrease in left ventricular ejection fraction (LVEF). Overall survival and progression-free survival were also assessed. **Results:** Mean treatment duration was 30 weeks; 107 patients (36.5%) discontinued therapy during the study, mainly due to disease progression (n = 86; 29.4%). A total of 78 SAEs were reported from 47 patients; the most frequently reported was diarrhoea (13 reports). Treatment had a relatively small effect on LVEF. Decreases were minor (0 to < 20%) in 61% of patients at the end of the study. During the study, 3 patients had decreased LVEF meeting the definition of an SAE; these events all resolved. Median overall and median progression-free survival were 37.6 and 21.1 weeks, respectively. **Conclusions:** Heavily pretreated patients with ErbB2-positive locally advanced or metastatic breast cancer may benefit from treatment with lapatinib and capecitabine, with a low risk of cardiac toxicity.

Zusammenfassung

Hintergrund: Im Rahmen des Lapatinib-Expanded-Access-Programmes (LEAP) erhielten Patienten aus 45 Ländern mit ErbB2 (HER-2)-positivem, metastasierten oder lokal fortgeschrittenen Mammakarzinom, die bereits mit Anthrazyklinen, Taxanen und Trastuzumab vorbehandelt waren, eine Kombinationstherapie aus Lapatinib und Capecitabin. Wir berichten hier die Ergebnisse der Patientengruppe aus 12 Ländern in Zentral- und Osteuropa. **Patienten und Methoden:** Bis zum 30. September 2008 wurden 293 Patienten aufgenommen. Die Sicherheit wurde mit Fokus auf schwerwiegende Nebenwirkungen (serious adverse events, SAE) und die linksventrikuläre Auswurffraktion (left ventricular ejection fraction, LVEF) kontrolliert; weiterhin wurden Daten für Gesamtüberleben und progressionsfreies Überleben erhoben. **Ergebnisse:** Die durchschnittliche Behandlungsdauer lag bei 30 Wochen; 107 Patienten (36,5%) beendeten die Therapie im Verlauf der Studie, hauptsächlich wegen Progredienz der Tumorerkrankung (n = 86; 29,4%). Bei 47 Patienten traten insgesamt 78 SAEs auf, am häufigsten Diarrhoe (13 Berichte). Bei 61% der Patienten zeigte sich eine Abnahme von 0 bis < 20% der LVEF am Ende der Studie. Bei 3 Patienten erfüllte die Abnahme der LVEF die Kriterien für einen SAE, alle normalisierten sich. Das mittlere Gesamtüberleben und progressionsfreie Überleben waren 37,6 Wochen bzw. 21,1 Wochen. **Schlussfolgerungen:** Vorbehandelte Patienten mit ErbB2-positivem, metastasierten oder lokal fortgeschrittenen Mammakarzinom können von einer Behandlung mit Lapatinib und Capecitabin profitieren, bei gleichzeitig geringem kardialen Toxizitätsrisiko.

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Introduction

Breast cancer is the most common type of cancer in women in Europe, and indeed worldwide. Despite continuous advances in the diagnosis and treatment of breast cancer, 131,900 women die of advanced or metastatic breast cancer in Europe every year, making up 17.5% of all cancer deaths in Europe [1]. Central and Eastern Europe (CEE) appears to have slightly lower incidence and mortality rates for breast cancer than Western and Northern Europe, possibly due to a different distribution of known risk factors such as postponement or avoidance of childbearing, hormonal contraception, hormone replacement therapy, changes in menstrual history, and obesity [2].

One of the most aggressive forms of breast cancer is associated with the overexpression of the ErbB2 (HER-2) receptor and/or amplification of the c-erbB2 gene. This abnormality is believed to be present in about 20% of breast cancer patients [3]; limited and sometimes anecdotal information suggests a similar proportion of ErbB2-positive patients in individual countries in CEE. For example, a rate of 14.7% has been reported in Slovenia [4]. ErbB2 positivity is associated with poor survival prognosis in untreated breast cancer [5], and with relative resistance to endocrine therapy in general or to certain types of endocrine therapy or chemotherapy [6, 7]. More recent studies suggest that ErbB2 positivity may be predictive of a differential and sometimes better response to certain regimens [8, 9]. Until recently, the only targeted treatment available specifically for ErbB2-positive breast cancer was the monoclonal antibody trastuzumab. However, many patients still relapse after treatment with trastuzumab; furthermore, its use has been associated with cardiac toxicity [10].

Lapatinib (Tykerb/Tyverb™, GlaxoSmithKline GmbH & Co KG, Munich, Germany), a small-molecule dual tyrosine kinase inhibitor, targets both ErbB2 and ErbB1 receptors, and appears to have lower cardiac toxicity than trastuzumab [11]. The efficacy and safety of lapatinib has been demonstrated in several studies of patients with metastatic breast cancer [12–15]. Interim analyses of a phase 3 study (EGF100151) of lapatinib in combination with capecitabine in patients with ErbB2-positive and advanced or metastatic breast cancer showed improved time to progression, progression-free survival (PFS), objective response rate, and clinical benefit rate, without a significant increase in toxicity compared with capecitabine monotherapy [12, 13]. The study was halted early by the independent data monitoring committee because superiority on the primary endpoint of time to progression was demonstrated by the group receiving lapatinib in combination with capecitabine. The results of the EGF100151 clinical trial generated demand for patient access to lapatinib before marketing approval. A global Lapatinib Expanded Access Program (LEAP) was therefore initiated to provide potential clinical benefit to patients with ErbB2-overexpressing breast cancer, who had previously received anthracyclines, taxanes and trastuzumab, and who were not eligible for another ongoing lapatinib clinical trial. A total of 45 countries worldwide were included in this initiative. The primary purpose of LEAP was to provide access to lapatinib, but safety and efficacy data were also collected. The results for the global population involved in LEAP up to 30 September 2008 have been reported [16]. This paper presents the results of a subanalysis of 293 patients enrolled in 12 CEE countries that participated in LEAP.

Patients and Methods

Objectives

The primary objective of the LEAP initiative was to offer pre-approval access to lapatinib in combination with capecitabine, to provide potential benefit to patients with ErbB2-overexpressing breast cancer refractory to treatment with anthracyclines, taxanes and trastuzumab. The secondary objective was to evaluate serious adverse events (SAEs) associated with this combination therapy in this population of patients.

Design

This was a single-arm, open-label, expanded-access study of lapatinib in combination with capecitabine in patients with locally advanced or metastatic breast cancer with ErbB2-positive tumours and disease progression following prior treatment regimens with anthracycline, taxane and trastuzumab. The study was conducted worldwide and was initiated on a per-country basis in countries where the application for a marketing licence had been submitted.

Main Inclusion and Exclusion Criteria

Patients aged ≥ 18 years with locally advanced (stage IIIb or stage IIIc with T4 lesion) or metastatic (stage IV) breast cancer and ErbB2-positive tumours were eligible. All patients had to have disease progression following prior therapy with an anthracycline, a taxane and trastuzumab. Patients had to have adequate haematological, hepatic and renal function, left ventricular ejection fraction (LVEF) within the institution's limit of normal (or > 50%) at baseline, as measured by echocardiogram or multigated acquisition (MUGA) scans, and a life expectancy > 8 weeks. Patients with central nervous system metastases were eligible if they did not require prohibited medications. The protocol was later amended to allow glucocorticoids for neurological signs and symptoms of central nervous system metastases. Prior treatment with hormonal therapy, lapatinib (i.e. as part of another clinical trial) or capecitabine (i.e. as previous agent or a non-lapatinib-containing regimen) was also permitted. Patients eligible for other ongoing lapatinib clinical trials were not permitted to enrol in LEAP. All included patients signed informed consent forms. The following were exclusion criteria: pregnancy or lactation at any time during the study; any disease significantly affecting gastrointestinal function; unresolved or unstable serious toxicity from previous cancer treatment; uncontrolled infection; inability to give informed consent; or active cardiac disease. Patients were also excluded if they were receiving concurrent chemotherapy (other than capecitabine), radiation therapy, immunotherapy, biological therapy (including ErbB1 and/or ErbB2 inhibitors), or endocrine therapy.

Treatment

Patients received lapatinib 1,250 mg/day and capecitabine 2,000 mg/m^2/day, both orally. Lapatinib was taken at approximately the same time every morning. The capecitabine dose was divided and taken once in the morning and once in the evening, about 12 h apart, for 2 weeks, followed

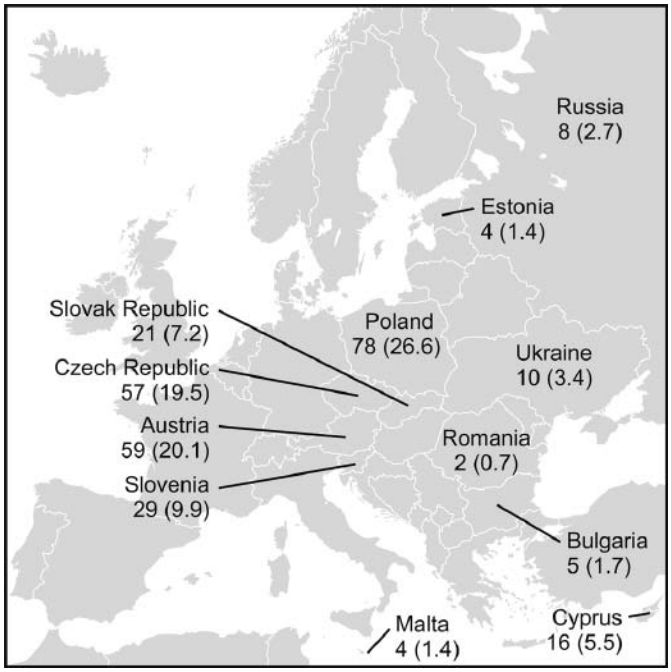

Fig. 1. Number (%) of patients from countries participating in LEAP in Central and Eastern Europe.

by a 1-week drug-free period. Dose reductions and delays for toxic effects due to either drug were permitted. Treatment was administered until either disease progression or withdrawal from study due to unacceptable toxicity or other reasons.

Assessments

Patients were monitored for SAEs; these included any event that was fatal, life-threatening, disabling or incapacitating, resulted in hospitalisation/prolongation of hospital stay, or was associated with congenital abnormality. SAEs were summarised and categorised by toxicity grade. Treatment toxicity was assessed by clinical and laboratory parameters. Safety and efficacy assessments were performed every 3 and 6 weeks, respectively, and at the end of treatment. LVEF was evaluated using echocardiograms or MUGA scans, performed at baseline, 6 weeks, 12 weeks, and then at 12-weekly intervals. LVEF (%) was summarised at each assessment. Both the absolute change from baseline and the relative percentage change from baseline were summarised according to the following categories: any increase, 0 to < 20% decrease, ≥ 20% decrease, or ≥ 20% decrease and below the lower limit of normal. For monitoring cardiac safety, the protocol defined a decrease in LVEF ≥ 20% and below the institutional lower limit of normal, or National Cancer Institute Common Toxicity Criteria (NCI CTC) grade 3 or 4 left ventricular systolic dysfunction, as an SAEs. Disease progression was determined by the modified Response Evaluation Criteria In Solid Tumors (RECIST) [17].

Statistics

No formal hypothesis was tested, as the primary objective was to make lapatinib available. However, PFS and overall survival were assessed. Overall survival was defined as the time from initiation of study medication until death due to any cause. PFS was defined as the time from initiation of study medication until the earliest date of disease progression or death from any cause. The protocol was amended in June 2008 to remove the PFS and overall survival endpoints because data collection ceased in countries where the combination received regulatory approval. Therefore, PFS and overall survival were censored if patients did not have disease progression or were alive by this date.

Table 1. Patient demographics (n = 293)

Parameter	
Age, years	
Mean (SD)	51.7 (10.34)
Median (range)	52.0 (27–77)
Sex[a], n	
Male/female	1/290
Race, %	
White or Caucasian/Arabic or North African	99.3/0.7
Prior capecitabine therapy[a], n	
Yes/no	98/194
Duration of therapy, weeks	
Mean (SD)	30.76 (20.96)
Median (range)	25.9 (1.0–83.9)

[a]Data not available for all patients.
SD = Standard deviation.

Table 2. Reasons for therapy discontinuation or withdrawal from the study

Description	Patients, n (%)
Enrolled (safety population)	293 (100)
Discontinued study drug	107 (36.5)
Adverse event/serious adverse event	11 (3.8)
Subject decided to withdraw	6 (2.0)
Progressive disease	86 (29.4)
Other	4 (1.4)
Did not remain in study for reasons other than drug discontinuation	72 (24.6)
Lost to follow-up	3 (1.0)
Death	59 (20.1)
Transitioned to commercial supply of lapatinib	1 (0.3)
Missing	9 (3.1)

Results

Patient Population

LEAP was implemented in June 2006. As LEAP is ongoing, the SAE and efficacy analyses reported here are based on the data-cut of 30 September 2008. A total of 293 patients with locally advanced or metastatic breast cancer were enrolled from 12 CEE countries (fig. 1). Both the mean and median age of the patients was 52 years, with the age ranging from 22 to 77 years. About a third of the patients (33.6%) had received prior capecitabine therapy (table 1). The mean duration of lapatinib plus capecitabine treatment in LEAP in CEE was 30 weeks, and the maximum duration of treatment was 83.9 weeks. A total of 107 patients (36.5%) discontinued therapy during the study, the majority due to disease progression (n = 86; 29.4%). In addition, 72 patients (24.6%) withdrew from the study, the majority due to death (n = 59; 20.1%) (table 2). There were no reports of accidental overdoses of lapatinib.

Safety

A total of 78 SAEs were reported from 47 patients. The most frequently reported SAE was diarrhoea (13 reports of which 11 were assessed as drug-related). Overall, 45% (35/78) of the SAEs reported were assessed as related by the investigator. The SAEs reported more than once are shown in table 3. There were 7 reports of SAEs with a fatal outcome, one of which was assessed as possibly related to lapatinib and capecitabine administration but was also considered possibly due to the breast cancer; the remaining 6 fatal events were considered not related to the study drugs.

SAEs of Special Interest

Cardiac Safety

Treatment with lapatinib plus capecitabine had a relatively small effect on LVEF. Mean LVEF values by scheduled visit are shown in figure 2. In most patients (71/116; 61%), the decreases in LVEF were minor (0 to < 20%) at the end of the study. During the entire study period, only 6/118 patients (5%) experienced a decrease of ≥ 20% in LVEF relative to baseline (table 4). Three patients had decreased LVEF that met the protocol-specified serious definition, yielding an incidence of 1.0% (3/293). However, by the end of treatment, there were no patients with an LVEF decrease ≥ 20% relative to baseline and below the institutional normal limits. The 3 patients who met the protocol-specified definition of a serious cardiac adverse event (either a decrease in LVEF ≥ 20% and below the institutional lower limit of normal, or grade 3 or 4 left ventricular systolic dysfunction) experienced decreases of 33, 31 and 23%, respectively. In all 3 cases, the event was asymptomatic, and treatment with capecitabine and lapatinib was interrupted. The first of these 3 subjects was treated with ramipril, and the other 2 patients did not require any treatment. In the first 2 cases, the event resolved and lapatinib and capecitabine were restarted without recurrence. In the third case, the event also resolved, but information on continued treatment was not provided.

Interstitial Pneumonitis and Hepatobiliary Events

No pulmonary SAEs were reported. Only 3 serious hepatobiliary events were reported, one of which was assessed as possibly related to lapatinib and capecitabine.

Table 3. Serious adverse events (SAEs) that were reported more than once in the Central and Eastern Europe cohort of LEAP (n = 293)

SAE	Drug-related SAEs, n (%)[a]	Total SAEs (all causalities), n (%)[a]
Diarrhoea	11 (14.1)	13 (16.7)
Vomiting	4 (5.1)	4 (5.1)
Anaemia	0	4 (5.1)
Thermal burn	0	4 (5.1)
Ejection fraction decrease	3 (3.8)	3 (3.8)
Nausea	2 (2.6)	2 (2.6)
Palmar-plantar erythrodysaesthesia syndrome	2 (2.6)	2 (2.6)
Brain oedema	0	2 (2.6)
Epilepsy	0	2 (2.6)

[a]Expressed as a percentage of all SAEs

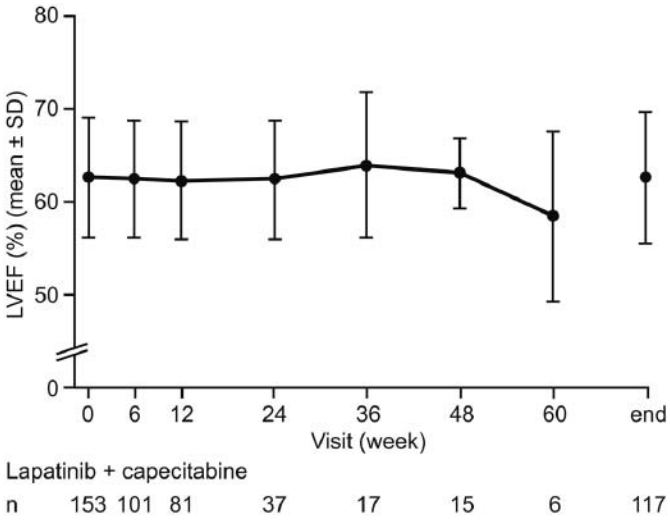

Fig. 2. Left ventricular ejection fraction (LVEF) values by scheduled visit (mean ± standard deviation).

Table 4. Relative percentage change in left ventricular ejection fraction (LVEF) from baseline by scheduled visit

	Patients, n (%)			
	total	0 to ≤ 20% decrease	≥ 20% decrease	≥ 20% decrease and below LLN
Week 6	100	69 (69)	1 (1)	0
Week 12	80	48 (60)	2 (3)	0
Week 24	36	21 (58)	0	1 (3)
Week 36	16	5 (31)	1 (6)	1 (6)
Week 48	14	8 (57)	1 (7)	0
Week 60	5	4 (80)	0	0
End of study	116	71 (61)	3 (3)	0
Any occurrence post-baseline	118	not reported	6 (5)	2 (2)

LLN = Lower limit of normal.

Efficacy

By the cut-off date of 30 September 2008, 59 patients (22.3%) had died and 205 patients (77.7%) were censored. The median overall survival was 37.6 weeks (95% confidence interval (CI) 33.0–47.9). With respect to PFS, 90 patients (34.1%) experienced disease progression or died and 174 (65.9%) were censored. The median PFS was 21.1 weeks (95% CI 16.3–25.7).

Discussion

Until recently, trastuzumab was the only targeted treatment available specifically for treating ErbB2-positive breast cancer. However, primary or secondary resistance occurs in many patients, and about 50% of patients with metastatic breast cancer treated with trastuzumab progress within 1 year of starting treatment [18]. It was therefore important to develop alternative therapies; lapatinib is one such alternative. This report of a CEE subgroup of LEAP confirms that treatment with lapatinib and capecitabine may benefit patients whose ErbB2-positive cancer has progressed despite pretreatment with an anthracycline, a taxane and trastuzumab. Other options for treating these patients include continued trastuzumab after progression, alone [19] or in combination with new agents such as DM1 [20] or pertuzumab [21]; or new agents on their own, for example neratinib [22].

Following the results of the EGF100151 clinical trial which showed improved PFS of patients treated with lapatinib plus capecitabine, LEAP was initiated. Expanded access programs allow treatments under investigation to be available before regulatory approval, particularly in patients who are likely to benefit and who have no other registered treatment options [23]. In addition, expanded access programs may allow the inclusion of patients who are not eligible for clinical trials, and thus provide important safety information.

The good safety profile of lapatinib found in this subgroup of CEE patients was consistent with the results of previous clinical studies [24, 25]. In the CEE cohort of LEAP, 45% of SAEs were considered as possibly related to the study drug; the proportion was slightly lower in the global LEAP results (38%) [16]. As in other studies of lapatinib, including the pivotal study by Geyer et al. [12], the most pronounced SAE, in both the global and CEE populations, was diarrhoea.

Cardiac toxicity is a well-known risk associated with trastuzumab [10]; cardiac function is therefore closely monitored in clinical trials with anti-ErbB2 agents. In this subgroup analysis of CEE countries enrolled in LEAP, as in the global cohort, treatment with lapatinib plus capecitabine appeared to have little effect on mean LVEF. In the CEE subgroup, 3/293 patients (1.0%) had a decreased LVEF that met the protocol-specified serious definition, compared with 21/4,283 patients (0.5%) in the global cohort. This low incidence of LVEF decrease is in line with previously reported findings with lapatinib. For example, in the study by Cameron et al. [13] (which was a follow-up report of the pivotal study by Geyer et al. [12]), there were no differences in mean LVEF between the capecitabine and the capecitabine plus lapatinib groups at scheduled assessments. Five patients in the combination group (n = 198) developed decreases in LVEF ≥ 20% and below the institution's limit of normal, but 4 of these were asymptomatic; all had returned to within the normal range at follow-up assessment, and lapatinib was not discontinued because of a decrease in LVEF in any patients. A meta-analysis of 44 trials of lapatinib with 3,689 patients also showed a low incidence of symptomatic and asymptomatic LVEF decrease (0.2 and 1.4%, respectively) [11].

Other adverse events considered possibly of particular importance were pulmonary toxicity, a known risk associated with ErbB1 inhibitors such as gefitinib [26], and hepatobiliary events. There were no pulmonary SAEs, and only 3 hepatobiliary SAEs were reported, one of which was assessed as possibly related to lapatinib or capecitabine.

Although a formal hypothesis was not tested in LEAP, the efficacy findings from the CEE cohort were similar to those for the global cohort of 45 countries [16]. By the cut-off date, 22.3% of patients in the CEE subgroup had died, compared with 29.4% in the global cohort. Median overall survival was 37.6 weeks (CEE) and 39.6 weeks (global), and median PFS was 21.1 weeks in both the CEE subgroup and the global cohort. In the EGF100151 trial, among patients treated with lapatinib plus capecitabine, median overall survival was 67.7 weeks and median time to progression (i.e. time from randomisation to disease progression or death from breast cancer) was 27.1 weeks [13]. These differences could be due to patients with poorer prognoses being allowed to enrol in LEAP. In addition, in contrast to EGF100151, LEAP enrolled patients with prior capecitabine exposure. Of course, caution must be exercised in comparing results across different trials because differences in the baseline population, prior regimens, treatment standards by country, and different study designs may all affect study outcomes. The slightly less restrictive inclusion criteria applied in LEAP compared with EGF100151 suggest that the patients enrolled in LEAP may be more indicative of the patient population actually treated in everyday clinical practice.

Conclusion

The results of the CEE subgroup analysis of LEAP confirm that patients with ErbB2-positive locally advanced or metastatic breast cancer, who have been previously treated with an anthracycline, a taxane and trastuzumab, may benefit from treatment with the combination of lapatinib and capecitabine, with a low risk of cardiac toxicity.

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Disclosure Statement

Meinolf Linn and Ash Das Gupta are employees of GlaxoSmithKline. The remaining authors have no relevant conflicts of interest to disclose.

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