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Phase I trial combining temozolomide plus lapatinib for the treatment of brain metastases in patients with HER2-positive metastatic breast cancer: the LAPTEM trial

E. de Azambuja[1*,†], D. Zardavas[1,†], M. Lemort[1], J. Rossari[2], C. Moulin[3], A. Buttice[1], V. D'Hondt[1], F. Lebrun[1], Y. Lalami[1], F. Cardoso[4], C. Sotiriou[1], T. Gil[1], D. Devriendt[1], M. Paesmans[1], M. Piccart-Gebhart[1] & A. Awada[1]

[1]*Breast Unit, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium;* [2]*Department of Oncology, Hospital Moinhos de Vento, Porto Alegre, Brazil;* [3]*Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;* [4]*Breast Cancer Unit, Champalimaud Cancer Center, Lisbon, Portugal*

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Background: Brain metastases (BMs) pose a clinical challenge in breast cancer (BC). Lapatinib or temozolomide showed activity in BM. Our study assessed the combination of both drugs as treatment for patients with HER2-positive BC and BM.

Methods: Eighteen patients were enrolled, with sixteen of them having recurrent or progressive BM. Any type of previous therapy was allowed, and disease was assessed by gadolinium (Gd)-enhanced magnetic resonance imaging (MRI). The primary end points were the evaluation of the dose-limiting toxicities (DLTs) and the determination of the maximum-tolerated dose (MTD). The secondary end points included objective response rate, clinical benefit and duration of response.

Results: The lapatinib–temozolomide regimen showed a favorable toxicity profile because the MTD could not be reached. The most common adverse events (AEs) were fatigue, diarrhea and constipation. Disease stabilization was achieved in 10 out of 15 assessable patients. The estimated median survival time for the 16 patients with BM reached 10.94 months (95% CI: 1.09–20.79), whereas the median progression-free survival time was 2.60 months [95% confidence interval (CI): 1.82–3.37].

Conclusions: The lapatinib–temozolomide combination is well tolerated. Preliminary evidence of clinical activity was observed in a heavily pretreated population, as indicated by the volumetric reductions occurring in brain lesions.

Key words: breast cancer, brain metastases, HER2, lapatinib, temozolomide

introduction

HER-2 overexpression is reported in ~20% of breast cancer (BC) patients, conferring aggressive biological [1, 2]. The treatment of patients with HER2-positive BC has been revolutionized by trastuzumab and lapatinib [3].

Brain metastatic dissemination remains an unresolved medical need, with BC being the second most common cause of brain metastases (BM) [4]. HER-2 positivity is a risk factor for BM in patients diagnosed with BC [5], with evidence supporting that trastuzumab-treated HER2 overexpressing metastatic BC bear an increased risk for BM [6]. The reasons for this are debatable: trastuzumab does not fully penetrate the intact blood–brain barrier (BBB), thus sparring cancer cells in the central nervous system (CNS) [7]. Alternatively, its high efficacy in controlling extracranial disease prolongs overall survival, turning the brain into a 'sanctuary' for metastatic disease [8].

Standard therapeutic options for BM include local approaches such as neurosurgical resection, stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT), with the role of systemic therapy being unclear.

Lapatinib as a small-molecule inhibitor can penetrate more efficiently the BBB [9]. Moreover, the lack of cross-resistance with trastuzumab promises efficacy in trastuzumab-pretreated patients [10–13].

Temozolomide is an alkylating agent, which has a lipophilic structure enabling BBB penetration. It has been tested in BM from different tumors either alone or in combination with capecitabine showing some activity [14–16].

Correspondence to: Dr Evandro de Azambuja, Br.E.A.S.T. Data Centre, Jules Bordet Institute, Blvd de Waterloo, 121 (7th Floor), 1000 Brussels, Belgium. Tel: +32-02-541-7244; Fax: +32-02-541-3477; E-mail: evandro.azambuja@bordet.be

†EDA and DZ contributed equally to this work.

In our trial (NCT00614978), we studied the combination of lapatinib and temozolomide in patients with HER2-positive BC presenting BM.

materials and methods

eligibility

This study was conducted at the Jules Bordet Institute (IJB), Brussels, Belgium. All patients enrolled received lapatinib combined with temozolomide. Eligibility criteria are published online only.

study design

This was an open-label phase I study. The primary end point was to evaluate the dose-limiting toxicities (DLTs) and determine the maximum-tolerated dose (MTD) of lapatinib plus temozolomide (supplementary Table S1, available at *Annals of Oncology* online). The secondary end point was to evaluate their clinical activity.

Three to six subjects were enrolled in five dose cohorts (supplementary Table S2, available at *Annals of Oncology* online), with dose escalation following the classical '3 + 3' phase I trial design.

treatment planning

Temozolomide was given orally, once a day, at three dose levels: 100, 150 and 200 mg/m^2/day, days 1–5. Lapatinib was given orally, once a day at three dose levels: 1000, 1250, 1500 mg/day. Both agents were given until progression of the disease, intolerable toxicity or a maximum of six cycles, whichever came first. A cycle was defined as 28 days of therapy.

response assessments

Brain magnetic resonance imagings (MRIs) were obtained at study entry and every 8 weeks thereafter. They included volumetric, 3D-gradient echo T1-weighted images, before and 10–15 min after intravenous administration of Gd at a dose of 0.1 mmol/Kg body weight. The image assessments, carried out at IJB, were reviewed by one expert radiologist (ML) using both 2D measurement of the longest axial diameters and 3D volumetric measurement of the lesions using 3D segmentation software (VOXAR 3D® from Toshiba Medical Systems). A CNS objective response was defined as either a complete response (CR: disappearance of all target lesions) or a partial response (PR: at least a 30% decrease in the sum of the longest diameter of the target lesions). Progressive disease (PD) was defined as the occurrence of either a new lesion or a >20% increase in the sum of the longest diameter of the target lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference point the smallest sum of the longest diameter since the treatment started.

Treatment response outside of the CNS was evaluated by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.0) guidelines, but was not mandatory as per protocol and was carried out by the investigator as part of the patient's standard of care.

safety assessments

In the present study, adverse events (AEs) and/or adverse drug reactions were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0). Cardiac monitoring was carried out, with an LVEF assessment using either ECHO or MUGA scan at baseline and every 12 weeks thereafter.

statistical analysis

The study's sample size was determined according to the well-established current methodology used to design dose-finding studies in oncology ('3 + 3' design). The 'safety analyses set' of subjects consisted of all patients who received at least one dose of lapatinib and temozolomide. AEs were listed by cohort/dose-level and evaluation time point using descriptive statistics. The 'efficacy analysis set' of participants included all eligible patients who had received at least 28 days of therapy and who had at least one post-therapeutic assessment of disease status by MRI. The efficacy end points are listed per dose level and cycle using descriptive statistics.

results

patients

Eighteen HER2-positive metastatic BC patients were enrolled between January 2008 and May 2011. Demographic and clinical characteristics are displayed in Table 1. Sixteen patients showed at least one BM but, because of slow study accrual, two patients with no BM and no standard therapeutic options available were enrolled.

The median age of all patients was 50 years (range, 34–77 years). This was a heavily pretreated population, with a median of four prior regimens (range, 1–7).

Regarding CNS disease, all but three patients had received prior CNS irradiation, and one had received additionally SRS. Sixteen patients had multiple BM, whereas one patient started the study treatment before SRS. The distribution of patients according to the treatment dose levels is shown in Supplementary Table S2, available at *Annals of Oncology* online. The median treatment duration reached 64 days (range, 23–169 days), with a median of two cycles (range, one to six cycles). The study drugs were stopped because of disease progression ($n = 14$), AEs ($n = 3$) and death ($n = 1$).

side effects

The non-hematologic toxicity was mainly grade 2 or higher (Table 2), with the most common AEs being fatigue, diarrhea and constipation. The following grade 3 AEs were observed: diarrhea in one patient at dose level I resulting in treatment discontinuation; fatigue in three patients at dose levels I, III and V, respectively; an infection (port-a-cath associated bacteremia) in one patient at dose level IV resulting in study withdrawal; bacterial pneumonia in one patient at dose level V; nausea in one patient at dose level V, which was managed with medication.

Few hematologic AEs were reported (Table 2), with no neutropenic fever. Per protocol definition, the MTD was not reached and both agents can be administered combined fully dosed. One patient developed grade 3 thrombocytopenia while on her first cycle at dose level V, with no major bleeding event. However, the treatment was delayed for 2 weeks, which constituted the only DLT observed. After the first cycle, this patient developed combined grade 4 leukopenia/neutropenia, not constituting a DLT (duration <7 days).

In terms of cardiac safety, no major toxicity events were observed. Nine patients underwent a second cardiac monitoring at 12 weeks. None of them showed an LVEF <50% or an absolute LVEF drop >15%.

Table 1. Patient characteristics

Characteristic	No of patients	%
Age, years		
Median	50	
Range	34–77	
ECOG performance status		
0	1	6
1	16	89
2	1	6
Hormone receptor status from primary tumor		
Positive	10	56
Negative	8	44
No. of metastatic sites of disease		
Median	2	
Range	1–3	
Sites of disease		
Brain	16	89
Lung	5	28
Liver	4	22
Nodes	4	22
Bone	2	11
Pleura	2	11
Adrenals	1	6
Peritoneum	1	6
Prior chemotherapy regimens (with or without biological agents)		
Median	4	
Range	1–7	
Median time to recurrence and brain metastasis (months, range)		
Median time to recurrence	38.5 (0.0–163.1)	
Median time to brain metastasis	60.8 (4.2–265.3)	
Prior chemotherapy regimens (with biological agents)		
Median	1	
Range	0–3	
Prior biological agents without chemotherapy		
Median	1	
Range	0–2	
Prior exposure to specific agents		
Trastuzumab	18	100
Anthracycline	18	100
Taxane	17	94
Capecitabine	12	67
Lapatinib	8	44
Vinorelbine	7	39
Platinum derivative	6	33
Prior CNS irradiation		
None	3	17
WBRT only	14	78
SRS only	0	0
WBRT and SRS	1	6

ECOG, Eastern Cooperative Oncology Group; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

Table 2. Toxicity by frequency

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total number of patients
Non-hematologic toxicity					
Fatigue	6	5	3	–	14
Diarrhea	5	3	1	–	9
Constipation	7	1	–	–	8
Anorexia	2	3	–	–	5
Headache	4	1	–	–	5
Vertigo	4	1	–	–	5
Nausea	3	–	1	–	4
Neuropathy	4	–	–	–	4
Vomiting	4	–	–	–	4
Abdominal pain	3	–	–	–	3
Articular pain	3	–	–	–	3
Dry skin	2	1	–	–	3
Dyspnea	3	–	–	–	3
Infection	1	–	1	–	2
Muscular pain	2	–	–	–	2
Cholestasis	1	–	–	–	1
Cognitive disturbance	1	–	–	–	1
Diabetes exacerbation	–	1	–	–	1
Dry mouth	1	–	–	–	1
Dysphagia	–	1	–	–	1
Epistaxis	1	–	–	–	1
Hyponatremia	1	–	–	–	1
Liver enzymes elevation	1	–	–	–	1
Pneumonia	–	–	1	–	1
Pleural effusion	–	1	–	–	1
Rash	1	–	–	–	1
Seizure	–	1	–	–	1
Stomatitis	1	–	–	–	1
Vision disturbances	2	–	–	–	2
Hematologic toxicity					
Anemia	6	–	–	–	6
Leukopenia	4	1	–	1	6
Neutropenia	–	–	1	1	2
Thrombocytopenia	4	–	1	–	5

tumor response

Evaluation of response using volumetric brain MRI was a secondary end point. Two patients did not have BM at baseline; a third patient received one cycle of treatment and stopped because of clinical PD. For the 15 remaining assessable patients, SD was achieved in 10 patients (67%) and PD in 5 patients (33%). The best response was in each case achieved after two or three cycles (one patient with SD was not assessed beyond two cycles).

The analysis of volumetric changes from the largest brain lesion was carried out in 13 patients (Figure 1A). Five patients out of the 18 were non-assessable for the purposes of this analysis: two had no BM at baseline, one had no reported volume at baseline and two had no measurements after baseline. For the same cohort of 13 patients, a separate volumetric changes analysis was undertaken using the sum of the volumetric measures of all lesions as calculated at baseline and at the follow-up brain MRI (Figure 1B). The relative evolution from baseline was calculated and the largest reduction was selected.

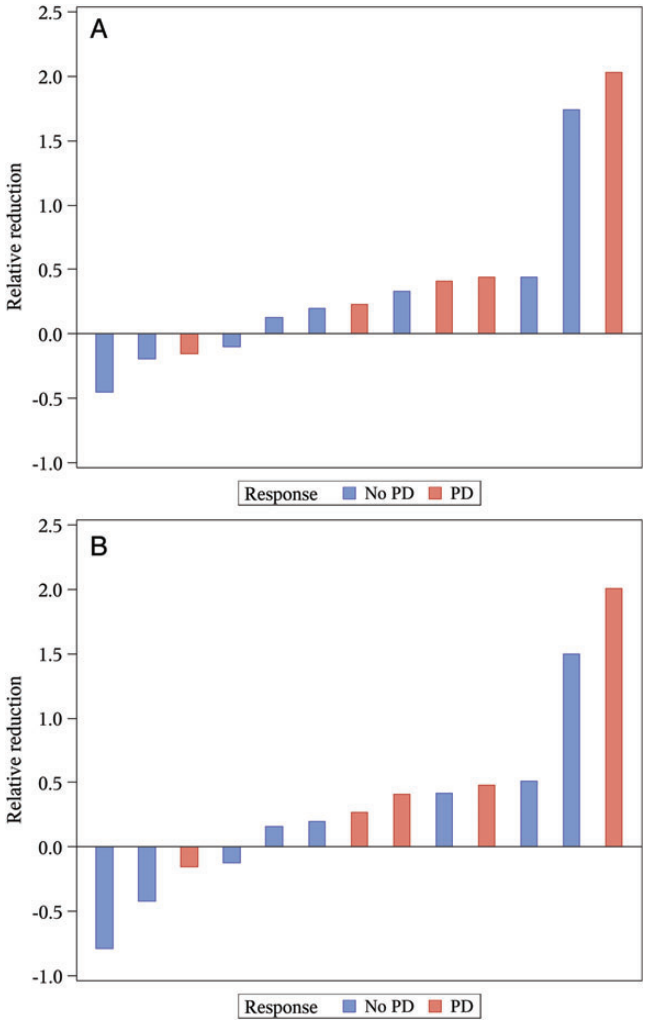

Figure 1. (**A**) Best relative volumetric change in the largest brain metastasis when compared with baseline. Each bar represents a patient having received a baseline and at least an 8-week volumetric brain magnetic resonance imaging (MRI) evaluation. Patients in red are those with progression as best response. The vertical *y*-axis represents a relative reduction in the largest brain metastasis (vol after treatment – Vol at baseline)/vol at baseline, with negativity corresponding to a reduction and positivity corresponding to an increase in the volume of the lesion. (**B**) Best relative volumetric change in the sum of the volumetric measures of all brain lesions. Each bar represents a patient having received a baseline and at least an 8-week volumetric brain MRI evaluation. Patients in red are those with progression as best response. The vertical *y*-axis represents a relative reduction in the sum of the volumetric measures of all brain lesions (sum vol after treatment – sum vol at baseline)/sum vol at baseline, with negativity corresponding to a reduction and positivity corresponding to an increase in the sum of the volumetric lesions.

Overall, as of 31 May 2012, all 18 patients experienced tumor progression. The estimated median progression-free survival was 2.60 months [95% confidence interval (CI): 1.78–3.42] for all 18 patients. It was also 2.60 months (95% CI: 1.82–3.37) for the 16 patients with BM. Death occurred in 14 patients, which corresponded to an estimated median survival time of 10.9 months (95% CI: 2.5–19.3) for all 18 patients, and 10.94 months (95% CI: 1.09–20.79) for the 16 patients with BM.

In terms of extracranial disease assessment, three patients showed SD of the brain but experienced extracranial PD after two, three and six cycles of treatment, respectively. Regarding the two patients without BM at study entry, one received six cycles and the other one cycle of the study treatment. Unfortunately, both the patients experienced systemic PD. However, the former of these latter two patients initially showed a metabolic PR of intrahepatic metastases on a PET scan.

discussion

This phase I study evaluated the safety of lapatinib combined with temozolomide in patients with HER2-positive BC and BM. This combination was found to be well tolerable.

Fatigue, diarrhea and constipation were the most frequent AEs. Hematologic toxicity was not frequent, and no cases of neutropenic fever or need for transfusions were reported. No cardiac toxicity was observed in assessable patients.

Preliminary efficacy data were generated in our study, with 10 out of 15 assessable patients achieving a SD (67%). The volumetric analyses carried out either for the sum of all BM or for the largest lesion indicated reductions in size, suggesting clinical benefit. With heavily pretreated patients in this study, including lapatinib pretreatment, it is conceivable that this element masked the efficacy of our regimen. Furthermore, all but one patient with BM had undergone local treatment consisting of WBRT and/or SRS.

Putting our trial in context with other relevant studies, we noted that in a retrospective analysis of patients treated with lapatinib combined with capecitabine, seven PRs were reported for BM, with three of these PRs achieved in the absence of prior local treatment [17]. Building on that concept, the LANDSCAPE trial assessed the use of lapatinib plus capecitabine before WBRT and found this to be an alternative to WBRT as front-line treatment [18]. Such an approach could substantially improve the quality of life of patients with BM by postponing the WBRT-induced cognitive deficit [19]. The results of the randomized phase III CEREBEL study, comparing the incidence of BM in patients with HER2-positive metastatic BC treated with lapatinib plus capecitabine versus trastuzumab plus capecitabine, have been presented [20]. CEREBEL did not show a decrease of the incidence of BM as site of first relapse for patients treated with the lapatinib–capecitabine compared with trastuzumab–capecitabine (8 versus 12 cases, $P = 0.360$). These results must be interpreted with caution, because the incidence of BM as the first site of progression in both arms was low [21].

WBRT combined with systemic treatment could be another approach, analogous to a trial in which WBRT was administered with a protracted low dose of oral vinorelbine and temozolomide in BC patients with newly diagnosed BM [22]. Out of 36 patients, 3 CRs and 16 PRs were reported (ORR of 52%), with a favorable toxicity profile. The advantage here is mainly that WBRT disrupts the BBB, thus potentiating a higher penetration of the systemic treatment in the brain [23]. Closely monitoring the dosing of the systemic agents to avoid excessive toxicity is essential.

Our study has some limitations such as the absence of neurocognitive function evaluation. However, our patient population was almost uniformly exposed to WBRT, and thus

the chance that the patients had already developed neurocognitive deficits is high. The volumetric changes analysis we undertook should be interpreted as exploratory, since no clinically meaningful thresholds for tumor reduction exist. However, in other trials volumetric reduction of CNS lesions has been associated with clinical benefit [11, 24].

In summary, this study proves the feasibility of treating patients with BM originating from HER2-positive BC with the combination of lapatinib and temozolomide at their single-agent recommended doses. Volumetric reductions in BM were also achieved. However, the lack of objective responses suggests limited antitumor activity of the regimen in this heavily pretreated population.

funding

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disclosure

EDA: Research Grant (GSK) and Travel Grant (GSK). FC: Honorarium Consultant (GSK) and Speakers Bureau (GSK). All the remaining authors have declared no conflicts of interest.

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