

Phase I Study of Intermittent High-Dose Lapatinib Alternating with Capecitabine for HER2-Positive Breast Cancer Patients with Central Nervous System Metastases



Aki Morikawa¹, Elisa de Stanchina², Elena Pentsova³, Margaret M. Kemeny⁴, Bob T. Li⁵, Kendrick Tang⁵, Sujata Patil⁶, Martin Fleisher⁷, Catherine Van Poznak¹, Larry Norton⁵, and Andrew D. Seidman⁵

Abstract

Purpose: Lapatinib and capecitabine cross the blood-tumor barrier in breast cancer brain metastasis but have modest clinical efficacy. Administration of high-dose tyrosine kinase inhibitor has been evaluated in brain metastases and primary brain tumors as a strategy to improve drug exposure in the central nervous system (CNS). We derived a rational drug scheduling of intermittent high-dose lapatinib alternating with capecitabine based on our preclinical data and Norton–Simon mathematical modeling. We tested this intermittent, sequential drug schedule in patients with breast cancer with CNS metastasis.

Patients and Methods: We conducted a phase I trial using an accelerated dose escalation design in patients with HER2-positive (HER2⁺) breast cancer with CNS metastasis. Lapatinib was given on day 1–3 and day 15–17 with capecitabine on

day 8–14 and day 22–28 on an every 28-day cycle. Lapatinib dose was escalated, and capecitabine given as a flat dose at 1,500 mg BID. Toxicity and efficacy were evaluated.

Results: Eleven patients were enrolled: brain only (4 patients, 36%), leptomeningeal (5 patients, 45%), and intramedullary spinal cord (2 patients, 18%). Grade 3 nausea and vomiting were dose-limiting toxicities. The MTD of lapatinib was 1,500 mg BID. Three patients remained on therapy for greater than 6 months.

Conclusions: High-dose lapatinib is tolerable when given intermittently and sequentially with capecitabine. Antitumor activity was noted in both CNS and non-CNS sites of disease. This novel administration regimen is feasible and efficacious in patients with HER2⁺ breast cancer with CNS metastasis and warrants further investigation.

Introduction

Central nervous system (CNS) metastases are associated with poor overall survival (OS) in patients with metastatic breast cancer (1–3). Patients with HER2-positive (HER2⁺) breast cancer have a higher incidence of CNS metastasis (2, 4). The advent of

anti-HER2-targeted therapy has changed the landscape for HER2⁺ metastatic breast cancers (MBC) with unprecedented improvement in OS associated with the introduction of newer HER2-targeted drugs such as pertuzumab and ado-trastuzumab-emtansine (5–7). However, management of CNS metastasis remains a clinical challenge in patients with HER2⁺ MBC. For example, among patients with HER2⁺ MBC treated with trastuzumab-emtansine (TDM-1), CNS was the first site of progression in 56% of patients with prior brain metastasis and 18% in those without prior brain metastasis (8). Isolated CNS progression, while maintaining disease control in non-CNS sites is not uncommon in this patient population (9, 10).

Because of the limited survival and unclear extent of blood-brain or blood-tumor barrier penetration, patients with CNS metastasis had, until recently, been historically excluded from clinical trials of systemic therapy (11). There are several trials conducted specifically in patients with brain metastasis, but there is a paucity of prospective trials for patients with other types of CNS involvement such as leptomeningeal or intramedullary spinal cord metastasis, where the median survival is much shorter compared with that of patients with brain metastasis (1, 12). There is a critical unmet need for novel effective systemic treatment in such patients (13).

Lapatinib and capecitabine have shown preclinical and clinical antitumor activity as monotherapy and in combination for MBC, and have been studied specifically in HER2⁺ brain

¹Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan. ²Antitumor Assessment Core Facility, Memorial Sloan Kettering Cancer Center, New York, New York. ³Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York. ⁴Queens Cancer Center of New York City Health and Hospitals, Queens, New York. ⁵Breast Cancer Medicine Service, Memorial Sloan Kettering Cancer Center, New York, New York. ⁶Department of Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York. ⁷Clinical Chemistry Service, Memorial Sloan Kettering Cancer Center, New York, New York.

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Corresponding Author: Andrew D. Seidman, Memorial Sloan Kettering Cancer Center, Evelyn H. Lauder Breast Cancer, 300 East 66th Street, New York, NY 10065. Phone: 646-888-4559; Fax: 646-888-4555; E-mail: seidmana@mskcc.org

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Translational Relevance

Treatment options for patients with breast cancer with central nervous system (CNS) metastasis are limited. Lapatinib and capecitabine have demonstrated CNS activity in HER2-positive (HER2⁺) breast cancer with brain metastasis. However, the clinical efficacy is limited, dosing has been empiric and based on conventional-labeled scheduling for each single agent, and the overlapping gastrointestinal toxicities from these drugs can be considerable. This study evaluated the safety and toxicities associated with intermittent high-dose lapatinib 3 days on/11 days off alternating with intermittent fixed dose capecitabine 7 days on/7 days off in patients with HER2⁺ breast cancer with CNS metastasis. This study is the first prospective trial to study the combination of lapatinib and capecitabine in patients with HER2⁺ breast cancer with leptomeningeal and intramedullary spinal cord metastasis. This regimen provides a rationally designed, tolerable alternative to conventional drug dosing and warrants further evaluation of its clinical efficacy.

metastases (14–17). We previously demonstrated the brain metastasis uptake of capecitabine, its metabolites, and lapatinib in patients with MBC undergoing clinically indicated craniotomy (18). The study showed detectable drug concentrations of both capecitabine and lapatinib in resected brain metastasis tissue. Although the concentration of 5-fluorouracil (the active metabolite of capecitabine) approached the cytotoxic inhibitory concentration, lapatinib concentration was variable and less optimal. This finding was consistent with the modest clinical activity reported in the clinical trials for brain metastasis (lapatinib monotherapy 2.6% and the combination ~38%; refs. 15, 17). Considering that the combination response rate noted in the brain metastases trial is comparable with the median response rate of 28% noted for capecitabine as a single agent in pretreated metastatic breast cancer without brain metastases (19), insufficient lapatinib uptake is a potential barrier to lapatinib or lapatinib capecitabine combination efficacy in the brain metastases population (20).

On the basis of our preclinical study (Supplementary Data S1) and studies reported by others (21–26), we hypothesize that a higher dose of lapatinib would improve the efficacy and drug penetration in CNS metastases (18, 23, 24, 27). However, given that both capecitabine and lapatinib are known to have overlapping gastrointestinal toxicities, high-dose lapatinib given in a standard concurrent administration would be too toxic. Intermittent dosing of capecitabine in a 7 days on/7 days off schedule has previously been shown to improve tolerance based on Norton–Simon mathematical modeling (28, 29).

We tested three intermittent dosing schedules against standard continuous dosing and found that there was no difference between the intermittent schedules (Supplementary Data S1). In addition, a higher tumor reduction was noted with intermittent high-dose administration compared with lower continuous dosing. Concurrent administration of capecitabine and high-dose lapatinib was not feasible due to prohibitive toxicity but sequential dosing appeared to be feasible. On the basis of these results, we derived a novel drug scheduling regimen that would allow administration of high-dose "pulsatile" lapatinib with

capecitabine using a xenograft model: high-dose lapatinib (3 days on/11 days off) given sequentially with intermittent capecitabine (7 days on/7 days off; refs. 27–29)¹. We chose to dose lapatinib twice daily to increase drug exposure (30). We conducted a phase I trial to test our hypothesis that this novel administration regimen will allow high-dose lapatinib administration in combination with capecitabine in patients with HER2⁺ MBC with CNS metastases.

Patients and Methods

This was a prospective multicenter phase I dose-escalation study in HER2⁺ MBC with CNS metastasis using an accelerated titration design (ClinicalTrials.gov Identifier: NCT02650752). The study sites included Memorial Sloan Kettering Cancer (New York, NY), Queens Cancer Center of Queens Hospital (Queens, NY), and the University of Michigan (Ann Arbor, MI). The study was conducted in accordance with the U.S. Common Rule. Appropriate approval was obtained from each institutional review board and in accordance with an assurance approved by the U.S. Department of Health and Human Services. Informed written consent was obtained from each subject. The primary objective of the study was to assess the toxicity and determine the MTD of the intermittent high-dose lapatinib alternating with capecitabine. Secondary and exploratory objectives included the clinical efficacy and feasibility of assessing circulating tumor cells (CTC) in cerebrospinal fluid (CSF) samples for patients with known or suspected leptomeningeal disease and compare CSF CTCs with blood CTCs.

The study included patients with HER2⁺ breast cancer as defined by IHC with the score of 3+, or if 2+ with confirmatory FISH ratio of ≥ 2.0 . Radiologic evidence of new or progressive parenchymal brain metastasis or leptomeningeal disease by MRI of the brain or spine or CSF cytology evidence of new or persistent leptomeningeal disease was required. The study was later amended to include new or progressive intramedullary spinal cord metastases, as this diagnosis was considered as CNS metastases. Prior lapatinib at a standard FDA-approved dose and capecitabine were allowed as long as capecitabine exposure was more than 6 months prior to the study enrollment. Patients must have received prior trastuzumab or chemotherapy for MBC unless the CNS was the only site of metastasis. Measurable disease was not required. Performance status between 0–2 on Eastern Cooperative Oncology Group (ECOG) scale was allowed. Patients must have had adequate organ function. Prior CNS-targeted therapies (including radiotherapy, surgery, or intrathecal therapy) were allowed.

¹Norton–Simon modeling is based on the Norton–Simon hypothesis: If N is the tumor size at the time of therapy and N' is the expected unperturbed growth rate at that size, then after therapy the perturbed growth (or regression) rate can be expressed as $(1-D)N'$, with slower than unperturbed growth when $0 < D < 1$ and tumor shrinkage when $D > 1$. Taking time t into account, a single dose of therapy results in a function $D(t) \geq 0$, which (if nonzero) reaches a maximum at some time after therapy before thereafter decreasing, sometimes to zero. The maxima $D'(T) = 0$ occurs at the time $T \geq t$ of maximum therapy effect, which would be the ideal time to introduce a different growth-perturbing therapy. Xenograft experiments with lapatinib confirmed a T of approximately 9 ± 1 days after three daily administrations. Prior published analyses of capecitabine confirmed a T of 9 ± 1 days after seven daily administrations. Pulsatile use of these agents allows dose escalations, thereby increasing their efficacy because for both agents there is a monotonically rising dose level–response relationship.

Study treatment

Cycle 1 = 28 days

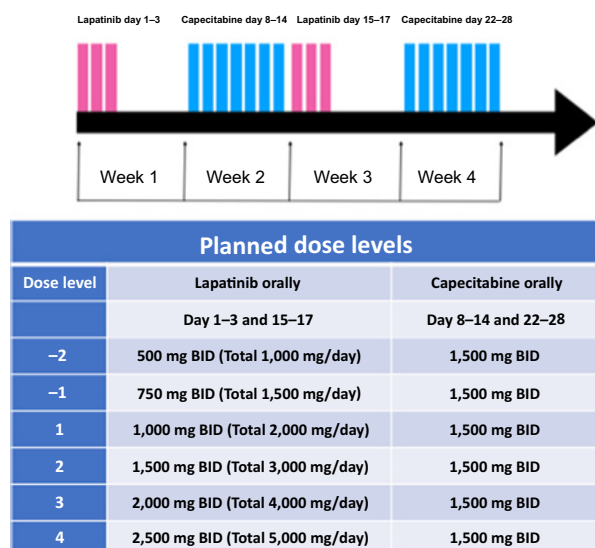


Figure 1.

Study treatment schema and planned drug dose levels: study treatment schema showing lapatinib 3 days on/11 days off alternating with capecitabine 7 days on/7 days off.

Study design

The study used an accelerated titration design for lapatinib dose escalation. No dose escalation was conducted for capecitabine. No inpatient dose escalation was allowed. Lapatinib dose levels consisted of 1,000 mg twice a day (BID), 1,500 mg BID, 2,000 mg BID, and 2,500 mg BID. Lapatinib was given BID for 3 days followed by 11 days of rest based on the Norton–Simon modeling and our preclinical study (27). Patients received lapatinib on days 1–3 and days 15–17 alternating with intermittent capecitabine as shown in Fig. 1. Capecitabine was administered as flat dosing of 1,500 mg oral BID for 7 days followed by 7 days of rest according to the Norton–Simon modeling as published previously (28, 29). Verbal and written diarrheal management instruction along with a prescription for loperamide was provided at the start of the study. However, no scheduled or required the prophylactic use of supportive medications, including antiemetics was prescribed as a part of the study treatment. Patients were allowed to continue concurrent intravenous (IV) trastuzumab or endocrine therapy if they were previously treated with the same drug.

A cycle was defined as 4 weeks in duration, and the dose-limiting toxicity (DLT) was defined and assessed during cycle 1. Patients continued treatment until progression of the disease, unacceptable toxicity, or withdrawal from the study. Dose reductions were allowed for lapatinib (maximum of two dose reductions in 500 mg per day increments) and capecitabine (maximum of two dose reductions by 500 mg per day increments).

Study assessments

Patients were assessed weekly during cycle 1 (for 4 weeks) and then every 4 weeks. Patient history, physical examination, and laboratory tests were performed at each visit. A review of medication compliance was conducted with a pill diary weekly for the first cycle and at the start of each subsequent cycle.

Toxicity was graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0. DLT was defined as the following toxicities attributable to study treatment during cycle 1: any grade ≥ 3 nonhematologic toxicity (except alopecia, altered taste, nail changes), and any grade 3 nausea, vomiting, or dehydration (except those occurred in setting of inadequate compliance with supportive care measures lasting for less than 48 hours), grade 3 diarrhea not responsive to supportive care measures within 72 hours, grade 4 neutropenia lasting ≥ 5 days in duration or with fever >38.5 and/or infection requiring antibiotic or antifungal therapy, grade 4 thrombocytopenia, and grade 4 anemia. Any unresolved drug-related toxicity requiring drug interruption for >14 days in the first cycle and any drug-related toxicity leading to a dose modification of lapatinib in the first cycle were also considered as DLT.

All patients were required to undergo baseline radiologic assessment with CT of chest/abdomen/pelvis and MRI of brain and spine with contrast. Imaging was performed every 8 weeks for the first 6 months and subsequently every 12 weeks with a CT scan and MRI brain. MRI spine was required at baseline for all but follow-up MRI spine was required only for patients with spinal cord metastasis or leptomeningeal disease. Patients with brain metastasis with measurable disease (defined as a lesion ≥ 1 cm) were evaluated for CNS response with or without non-CNS response (depending on the site of measurable disease). For patients with brain metastasis, CNS RECIST 1.1 and RECIST 1.1 criteria were used to evaluate target lesions. For patients with leptomeningeal disease, responses were assessed by CSF cytology, radiology imaging, and clinical signs/symptoms. Complete response was defined by complete cytologic and radiologic response with stable or improved clinical function. Partial response was defined as either complete cytologic with stable imaging or complete radiologic response with stable cytology and at least stable clinical function. Progressive disease was defined as either radiologic progression or worsening clinical signs/symptoms or new clinical signs/symptoms attributable to leptomeningeal disease and warrant a change in therapy per the treating investigator. Stable disease was defined as a response that did not meet complete, partial, or progressive disease response criteria for patients with leptomeningeal disease as described above.

Patients with leptomeningeal disease with no contraindication to CSF collection were approached for a CSF biomarker collection. For consenting patients with leptomeningeal disease, CSF was collected for routine cytology, CSF CTC and blood CTC at baseline, cycle 2 day 1, cycle 3 day 1 then every 8 weeks for the first 6 months and subsequently every 12 weeks. CSF (3.5 mL) and 7.5 mL of whole blood were collected in CellSave Tubes (Veridex LLC) and shipped to the central study laboratory (Dr. Martin Fleisher, Memorial Sloan Kettering, New York, NY) within 48 hours of collection. The CellSearch (Menarini Silicon Biosystems) platform was used to enumerate CTCs in CSF and serum specimens. Results were reported as number of CTCs per 3 mL of CSF (CSF CTCs/3 mL) and as number of CTCs per 7.5 mL of blood.

Statistical analysis

MTD was determined using an accelerated titration design without inpatient dose escalation. In the accelerated titration design, 1 patient was accrued per each sequential dose cohort until one DLT or two instances of moderate toxicity were observed. After such an observation, the study reverts to a traditional 3+3 design. Toxicity data were summarized with descriptive statistics. If a patient withdrew or discontinued the study drugs prior to day 29 due to reasons unrelated to adverse events, death, or progression of the disease, an additional patient was allowed to enroll and replace that patient. However, if a patient had any dose of study drug, that patient was included in the study analysis including toxicity and DLT assessments.

Initially, for those patients with measurable disease, response rate, progression-free survival, and OS were considered as exploratory objectives. However, after the completion of enrollment, the study population consisted of various CNS metastasis types (brain metastasis, leptomeningeal disease, and spinal cord metastasis) with the differing historical clinical outcome. Therefore, we present the exploratory clinical outcomes in a graphical format.

Results

Patients

From February 2016 to June 2017, 11 patients were enrolled. The clinical characteristics of all patients are summarized in Table 1. One patient came off study due to noncompliance after three doses of lapatinib, and an additional patient was enrolled to fill that dose level per the protocol. There were 4 patients with parenchymal brain metastasis only, 5 patients with leptomeningeal disease (2 of which had concurrent brain metastasis), and 2 patients with spinal cord metastasis with concurrent brain metastasis or brain metastasis and leptomeningeal disease.

All but two had prior radiotherapy for CNS metastasis. Three patients (27%) had prior capecitabine, and 2 patients (18%) had prior lapatinib exposure. Of the 5 patients with leptomeningeal disease, 3 had prior intrathecal/intraventricular therapy that included IT trastuzumab, IT methotrexate, and/or IT topotecan.

Determination of the MTD and toxicities

During the accelerated titration portion, the dose was escalated up to 2,000 mg BID, at which point the 3+3 portion was triggered. In total, 1 patient was treated at the 1,000 mg BID lapatinib dose level without any DLT. There were no DLTs seen in 6 patients treated at the 1,500 mg BID lapatinib dose level. At the 2,000 mg BID dose, there were 4 patients treated and two DLTs: one grade 3 nausea and one grade 3 vomiting despite institution of and compliance with the supportive measure as specified in the protocol. One patient underwent one dose reduction to 1,500 mg BID as allowed per the protocol and subsequently remains on study to date. Another patient treated at 2,000 mg BID dose level came off study due to grade 3 nausea and discontinued treatment without dose reduction during the first cycle. The MTD was determined to be 1,500 mg BID lapatinib 3 days on/11 days off alternating with capecitabine 1,500 mg oral BID on 7 days on/7 days off.

All 11 patients (including the patient who came off study for noncompliance) were evaluable for toxicity. During the cycle 1, most common toxicities (>20%) regardless of attribution were grade 1 and 2 diarrhea (45.5% and 27.3%, respectively), grade 1 nausea (36.4%), grade 1 fatigue (27.3%), grade 2 vomiting (27.3%), and grade 1 palmar-plantar erythrodysesthesia (PPE, 27.3%). There were three grade 3 adverse events, which two were attributed to the study treatment (DLTs). The most common (>20%) treatment-emergent toxicities, regardless of attribution, were grade 2 vomiting, grade 1 and 2 diarrhea, grade 1 abdominal

Table 1. Patient characteristics (N = 11)

Characteristics		Number	Percentage	Median (range)
Age (years)				52 (34–75)
ECOG Performance status	0	2	18%	
	1	6	55%	
	2	3	27%	
ER/PR Receptor status	ER ⁺ /PR ⁺	3	27%	
	ER ⁺ /PR ⁻	2	18%	
	ER ⁻ /PR ⁻	6	55%	
CNS Metastasis type	Parenchymal BM only	4	36%	
	Leptomeninges ^a	5	45%	
	Spinal cord ^a	2	18%	
Non-CNS metastasis status ^b	Yes	6	55%	
	No	5	45%	
Previous CNS-targeted treatment	Surgery	1	9%	
	Radiation	9	82%	
	Intrathecal therapy	3	27%	
Previous capecitabine exposure	Yes	3	27%	
	No	8	73%	
Previous lapatinib exposure	Yes	2	18%	
	No	9	82%	
Prior anti-HER2 therapy (other than lapatinib)	IV Trastuzumab	11	100%	
	IT Trastuzumab	2	18%	
	IV Pertuzumab	8	73%	
	TDM-1	5	45%	

Abbreviations: BM, brain metastasis; CT CAP, computer tomography of chest/abdomen/pelvic; ER, estrogen receptor; N, sample size; NED, no evidence of active disease; PR, progesterone receptor.

^aPatients may have concurrent parenchymal brain metastasis and/or leptomeningeal metastasis.

^b"No" = no evidence of disease on CT CAP.

Table 2. Adverse events regardless of relationship to study treatment (occurring in >20% of treated patients, *N* = 11)

Adverse event	Maximum grade				Total <i>N</i> (%)
	1 <i>N</i> (%)	2 <i>N</i> (%)	3 <i>N</i> (%)	4 <i>N</i> (%)	
Diarrhea	5 (45%)	3 (27%)	1 (9%)	0 (0%)	9 (82%)
Nausea	3 (27%)	3 (27%)	1 (9%)	0 (0%)	7 (64%)
Vomiting	0 (0%)	6 (55%)	1 (9%)	0 (0%)	7 (64%)
Abdominal pain	4 (36%)	1 (9%)	0 (0%)	0 (0%)	5 (45%)
Anorexia	2 (18%)	2 (18%)	0 (0%)	0 (0%)	4 (36%)
Headache	4 (36%)	0 (0%)	0 (0%)	0 (0%)	4 (36%)
PPE	3 (27%)	1 (9%)	1 (9%)	0 (0%)	5 (45%)
Peripheral neuropathy	2 (18%)	1 (9%)	0 (0%)	0 (0%)	3 (27%)
Fatigue	4 (36%)	3 (27%)	0 (0%)	0 (0%)	7 (64%)
Generalized muscle weakness	0 (0%)	2 (18%)	1 (9%)	0 (0%)	3 (27%)
Back pain	2 (18%)	1 (9%)	0 (0%)	0 (0%)	3 (27%)

Abbreviation: *N*, number of patients.

pain, grade 1 and 2 fatigue, grade 1 headache, grade 1 and 2 nausea, and grade 1 PPE. Commonly reported toxicities (>20%) regardless of attribution to study treatment by maximum grade of toxicity per patient are summarized in Table 2.

Clinical activity

All 11 patients had baseline radiologic assessments. Two patients came off study prior to the first follow-up radiologic assessment (for noncompliance and toxicity). Three patients with parenchymal brain metastasis completed at least one cycle of study treatment and had a follow-up radiologic assessment. Of the 2 patients with brain metastasis with measurable target lesion, 1 had unconfirmed stable disease, and other had confirmed stable disease. Of the 4 patients with leptomeningeal disease who had completed at least one cycle of study treatment, 1 patient had a partial response and 1 had stable disease. One patient with multilevel intramedullary spinal cord metastases had significant, albeit transient improvement in sensory symptoms and motor symptoms resulting in improved functional status and ambulation.

The duration of therapy and reason for treatment discontinuation for each patient grouped by the CNS site of disease is summarized in Fig. 2. Five patients had CNS as the only site of detected disease (defined as no evidence of disease detect on non-CNS CT body imaging): PT 1, 3, 5, 12, and 13. Five patients continued intravenous trastuzumab as allowed by the protocol: PT 5, 6, 9, 10, and 14.

Three patients were on study treatment for at least 6 months. Two of 3 patients had leptomeningeal disease. One patient who came off study treatment after 7 months had prior exposure to intrathecal therapy (including intrathecal trastuzumab) and radiotherapy but not to capecitabine and lapatinib exposure. The patient (PT5) who has completed 22 cycles of study treatment to date did not have capecitabine, lapatinib, or intrathecal treatment prior to the study enrollment and remains on study. Another patient (PT12) who remains for more than 12 months on the study treatment had a progressive brain metastasis after CNS radiotherapy and had previously discontinued capecitabine and due to toxicity before the study entry.

As of April 2018, 2 patients remain on study treatment. Nine patients are off protocol therapy for the following reasons: progression of disease (6 patients), toxicity (1 patient), noncompliance (1 patient with leptomeningeal disease), and voluntary withdrawal (1 patient with brain metastasis). Of the 6 patients who came off study treatment for progression, CNS was the site of

progression for 5 patients (83%). There have been 4 deaths, all of which were unrelated to the study treatment.

Exploratory circulating cell analysis

Patients with leptomeningeal disease with or without spinal cord metastasis were approached for optional CSF and blood research collection for CTC analysis. Three patients (all with intraventricular reservoir) consented to the serial CSF and blood collection, and the data is summarized in Table 3. Two patients had leptomeningeal disease, and 1 patient had leptomeningeal disease and spinal cord metastasis. All had detectable CTCs per 3 mL of CSF at baseline (range: 2–328 CTCs/3 mL). Two patients with leptomeningeal disease had a baseline positive conventional CSF cytology, which became negative after one cycle of therapy. Concurrently, the number of CTCs decreased and remained detectable whereas CSF cytology was negative. Subsequently, the number of detectable CTCs in CSF increased as patients experienced the progression of CNS disease noted radiologically and clinically. The CTCs in blood were discordant with the CTCs in CSF for the patient with leptomeningeal disease (PT1) with no evidence of disease on non-CNS imaging, whereas the CTCs in CSF and blood similarly decreased for the patient with leptomeningeal disease who had disease present in both CNS and non-CNS imaging (PT14). For patient with leptomeningeal disease with spinal cord metastasis (PT10), the CTCs in CSF remained very low at baseline and subsequently, even when the disease progressed. Interestingly, this patient was taken off the study by the treating investigator for an increase in intramedullary metastases with expansile intramedullary edema.

Discussion

We evaluated the safety and toxicity of high-dose pulsatile lapatinib alternating with capecitabine in patients with HER2⁺ breast cancer with CNS metastasis. The MTD regimen was defined as lapatinib 1,500 mg BID on day 1–3 and day 15–17 with capecitabine 1,500 mg BID on day 8–14 and day 22–28 on an every 28-day cycle. Lapatinib and capecitabine combination has shown clinical activity in patients with HER2⁺ breast cancer in several phase II trials (14, 17). However, the degree of clinical activity has been limited. The trial was motivated by our previous observation made in our "window-of-opportunity" presurgical study, where we reported that capecitabine and lapatinib do cross the blood-tumor barrier but variably and suboptimally for

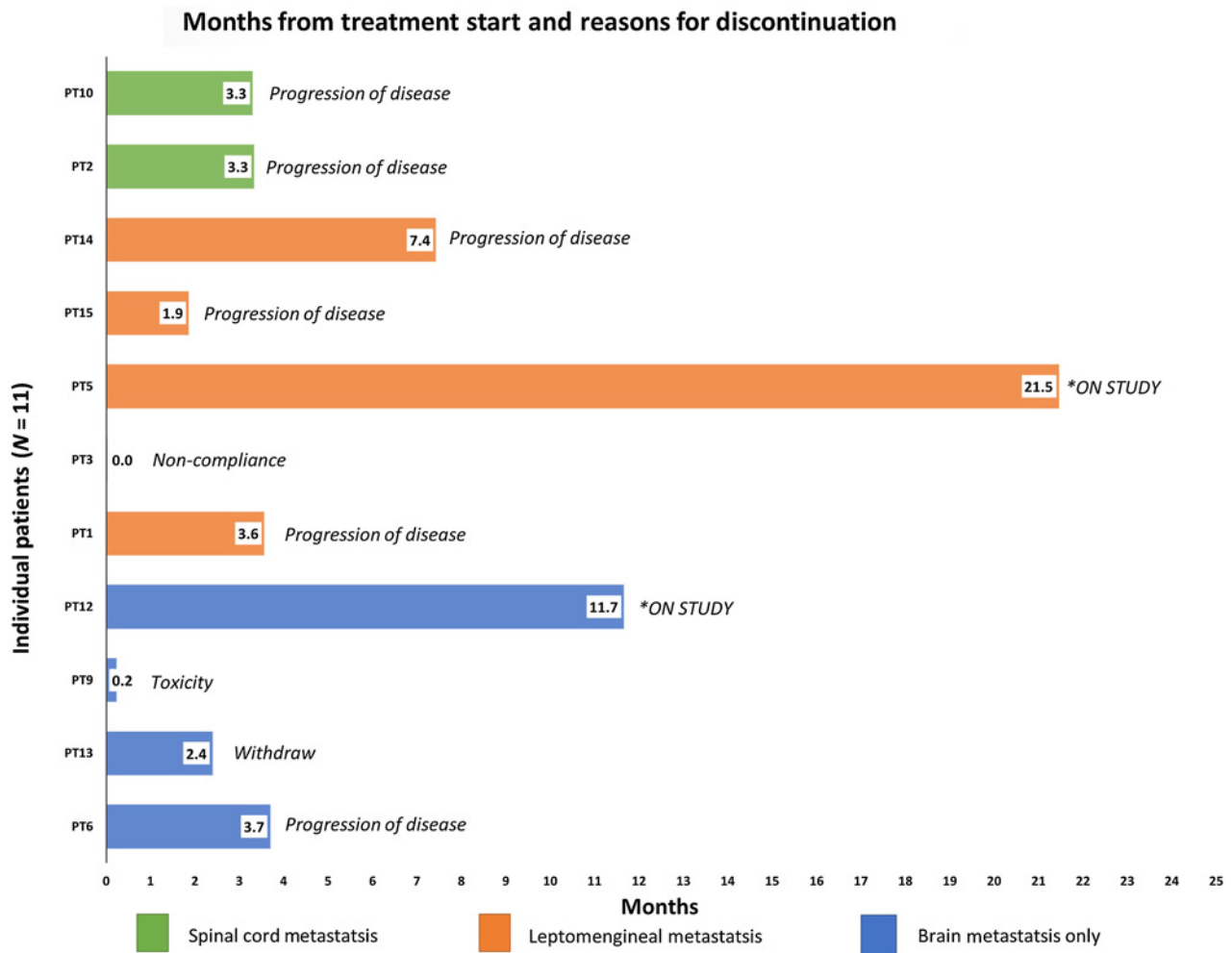


Figure 2. Treatment duration: the duration of on-study treatment per patient is shown for all 11 patients on the study. Sites of central nervous disease are indicated by color coding. Two patients remain on the study (the duration is at the time of data-lock).

Table 3. CTC analysis of matched CSF and blood

Patient PT1	Baseline	C2D1 ^a	C3D1 ^a			
CTC CSF	328	76	117			
CTC Blood	0	Not done	0			
CSF Cytology	Positive	Negative	Positive	CNS Progression/off study		
MRI Brain/spine	Lesions present	Not done	Stable			
CT CAP	No lesions	Not done	No lesions			
Patient PT14	Baseline	C2D1	C3D1	C5D1	C7D1	
CTC CSF	22	13	13	2	9	
CTC Blood	14	0	0	0	1	
CSF Cytology	Atypical/positive ^b	Negative	Atypical/negative ^b	Negative	Atypical/negative ^b	CNS Progression/off study
MRI Brain/spine	No lesions	Not done	Stable	Stable	Stable	
CT CAP	Lesions present	Not done	Stable	Stable	Stable	
Patient PT10 ^c	Baseline	C2D1	C3D1			
CTC CSF	2	3	1			
CTC Blood	0	1	0			
CSF Cytology	Suspicious/negative ^b	Negative	Negative	CNS Progression/off study		
MRI Brain/spine	Lesions present	Not done	Stable			
CT CAP	Lesions present	Not done	Stable			

Abbreviation: CT CAP, computer tomography of chest/abdomen/pelvis.

^aStudy specified assessments made prior to the start of cycle 2, 3, 5, and 7. Patients were taken off study for progression of disease based on nonstudy scheduled clinical, cytologic, or radiologic assessments made during clinical follow-up.

^bIf the CSF cytology was atypical or suspicious, a repeat CSF study was conducted for a confirmatory testing.

^cPT10 had concurrent brain and spinal cord metastases.

lapatinib (18), by mathematical modeling and xenograft studies (Supplementary Data).

We aimed to improve the clinical efficacy of these drugs which are already FDA approved, and whose toxicities are well characterized. The drugs have overlapping gastrointestinal toxicities that often make the combination therapy difficult to administer in clinical practice. We tested a dosing schedule that was designed on the basis of Norton–Simon mathematical modeling where we hypothesized that the pulsatile dosing and intermittent alternating scheduling of these drugs will improve tolerability and allow a higher dose of lapatinib to be administered (27). We then conducted a preclinical xenograft study, further informing the dosing schedule for this trial (Supplementary Data S1). In this trial, we translated and evaluated our preclinical finding that a high-dose of lapatinib given 3 days on/11 days off alternating with capecitabine 7 days on/7 days off would be tolerable in patients with breast cancer with CNS metastasis.

In the randomized phase II trial of capecitabine plus lapatinib or lapatinib plus topotecan in HER2⁺ breast cancer brain metastasis, of the 13 patients randomized to lapatinib (given 1,250 mg orally daily) with capecitabine (2,000 mg/m² BID on days 1–14 of a 21-day cycle), 23% experienced grade 3 and 8% had grade 4 diarrhea (17). Grade 3 PPE was reported in 15% of patients (17). Although we noted less grade 3 and 4 diarrhea and PPE, there was more grade 2 vomiting, which may have been partly due to the pill burden, and/or a CNS emetogenic effect of pulsatile high-dose lapatinib. Most recently, neratinib, another HER2-targeted tyrosine kinase inhibitor (TKI) was studied in combination with capecitabine for brain metastasis where grade 3 diarrhea occurred in 29% of patients (31). Therefore, we believe the tolerability of our study regimen is at least comparable with other reported TKI/capecitabine combinations.

Unfortunately, as this was a phase I trial with the primary objective of assessing safety and toxicity, we did not have many patients with measurable disease in each CNS metastasis type to meaningfully examine response rate or progression-free survival. Moreover, historically there were no standard criteria to assess response in leptomeningeal disease or intramedullary spinal cord metastasis. We used a study-specific leptomeningeal disease response criteria, but no response criteria was developed for spinal cord metastasis, as this patient population was not included at the time of study conception. Only recently, there is a proposal to standardize leptomeningeal disease response criteria in trials (32). Despite having a mixed population, we noted that 3 patients remained on study therapy for more than 6 months with 2 remaining on study for more than a year.

We conducted an exploratory comparative analysis of CTCs in CSF and blood. For the 3 patients with leptomeningeal disease who enrolled, CTCs in CSF were detectable even when conventional cytology was negative. The trajectory of changes in CTC enumeration correlated with the clinical course during the study for 2 patients. We also noted discordance between the detection of CTCs in CSF and blood that was reflective of the discordance between the CNS and non-CNS disease extent. Although the number of patients was very small for the CTC analysis, the finding warrants further evaluation of CTC analysis in CSF as a diagnostic and disease monitoring tool for patients with leptomeningeal disease. It is notable that for the patients with both leptomeningeal disease and spinal cord metastasis, CTCs was not informative. Of note, CSF was collected from an intraventricular reservoir for this patient, and it is unclear

whether the source of CSF collection may impact CTC detection in such case. The question remains whether CTC analysis in CSF is useful only in leptomeningeal disease or also in other types of CNS metastasis.

Our accelerated titration phase I design was efficient, thus resulting in a modest sample size of study patients to robustly ascertain clinical efficacy as a secondary endpoint. It is worth noting that there were patients who remained on study therapy for more than 6 months. In contrast, the recently reported phase II trial of intrathecal trastuzumab in patients with HER2⁺ leptomeningeal disease had a median progression-free survival of 2.4 months (33). In addition, the phase II trial of pertuzumab and high-dose trastuzumab (PATRICIA) reported median treatment duration of 4.4 months (range 1.2–8.3) among the 15 patients analyzed in the interim analysis (34). However, the clinical activity observed does not easily lend itself to comparison with historical controls or other trials, and as such, further phase II investigation is warranted.

We would propose that the next step is to evaluate clinical efficacy of this study regimen in a phase II setting (separate cohorts of patients with brain and leptomeningeal disease) randomized against a standard of care or physician's choice (which may include various anti-HER2 TKIs or non-TKIs but reported to have CNS activity such as TDM-1) to provide a contemporary benchmark. Moreover, the extent of clinical benefit associated with the intermittent high dose approach (rather than the specific regimen tested in this study) can be further evaluated and explored using newer anti-HER2 TKIs such as neratinib and tucatinib (31, 35). This may be more relevant for neratinib where diarrhea is a significant concern as mentioned above.

Our preclinical model showed a ceiling effect for lapatinib when given at a very high dose and did not allow sufficient evaluation of the additive value of capecitabine. In this study, we decided to optimize the combination regimen of lapatinib and capecitabine which is well-established with known CNS and non-CNS activity (36). A separate cohort of single agent lapatinib was considered during the conception of this study but ultimately not pursued partly due to prioritizing study efficiency and concern for tumor heterogeneity (unlike cell lines, clinical disease may consist of HER2-driven and non-HER2-driven cells) and a very modest activity of standard dose lapatinib single agent. However, a single-agent high-dose TKI is certainly a possible approach to explore to further mitigate toxicity and maximize clinical activity in the CNS as opposed to a combination with capecitabine especially for newer TKIs with more robust single-agent activity.

Although the epidemiology for patients with HER2⁺ brain metastasis has evolved with a more extended median survival, we previously reported that approximately 36% of patients with HER2⁺ brain metastasis present with CNS as the only site of active disease (10). Moreover, Le Scodan and colleagues reported that 61% of trastuzumab-treated patients with HER2⁺ brain metastasis ultimately died despite well controlled or no evidence of non-CNS disease (37). Therefore, the treatment of CNS metastasis in HER2⁺ patients remains an important clinical problem.

Leptomeningeal disease and intramedullary spinal metastasis are still associated with severely limited survival of only a few months (1, 12, 38), and such patients have limited therapeutic options. Although there are more therapeutic trials that include patients with brain metastasis, there is a paucity of prospective

trials that allows patients with progressive leptomeningeal disease. Moreover, to the best of our knowledge, there are no published prospective trial data for patients with progressive intramedullary spinal metastasis. This trial was uniquely inclusive in this regard in an effort to offer trials to patients who are traditionally excluded from clinical trials (11).

In summary, this study provides evidence that phase I evaluation of new regimens in patients with CNS metastases is feasible, and that optimized drug dosing and scheduling may mitigate toxicity while providing greater potential for efficacy in the CNS compartment. We are encouraged by the durable clinical activity observed in some of our patients. The study regimen and strategy warrants expanded evaluation in this population as supported by our data. Drug development and trial options for patients with CNS metastasis remain an area of urgent and unmet need.

Disclosure of Potential Conflicts of Interest

A. Morikawa reports receiving commercial research grants from Novartis, Lilly, Takeda/Millennium, Genentech, and Merrimack. E. Pentsova is a consultant/advisory board member for AstraZeneca. B.T. Li is a consultant/advisory board member for Genentech, Hengrui Therapeutics, and Mersana Therapeutics. A.D. Seidman reports receiving other commercial research support from Novartis and is a consultant/advisory board member for Puma. No potential conflicts of interest were disclosed by the other authors.

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Authors' Contributions

Conception and design: A. Morikawa, E. Pentsova, B.T. Li, S. Patil, L. Norton, A.D. Seidman

Development of methodology: A. Morikawa, E. de Stanchina, B.T. Li, M. Fleisher, L. Norton, A.D. Seidman

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Morikawa, E. de Stanchina, M.M. Kemeny, K. Tang, M. Fleisher, C. Van Poznak, A.D. Seidman

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Morikawa, E. Pentsova, B.T. Li, S. Patil, L. Norton, A.D. Seidman

Writing, review, and/or revision of the manuscript: A. Morikawa, E. Pentsova, M.M. Kemeny, B.T. Li, K. Tang, S. Patil, M. Fleisher, C. Van Poznak, L. Norton, A.D. Seidman

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Morikawa, K. Tang, A.D. Seidman

Study supervision: A. Morikawa, A.D. Seidman

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