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Full Length Article

All-oral combination of lapatinib and capecitabine in patients with brain metastases from HER2-positive breast cancer – A phase II study

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KEYWORDS

HER2-positive breast cancer;
Brain metastases;
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Abstract *Purpose:* Approximately one-third of patients with advanced, HER2 + ve breast cancer (BC) develop brain metastases (BMs). The aim of this study is to investigate efficacy and tolerability of the combination of lapatinib and capecitabine (LC) in HER2 + ve BC patients with brain metastases (BCBM).

Patients and methods: Between January 2011 and January 2013, 21 patients with HER2 + ve BCBM were included. Sixteen patients (76.19%) progressed after whole brain radiotherapy (WBRT) and 5 patients (23.81%) were treatment-naïve for BM. Patients received lapatinib (1250 mg/day continuously) and capecitabine (2000 mg/m^2 on days 1–14 of a 21-day cycle). All patients were treated with trastuzumab either in the adjuvant or metastatic setting. No patients had received prior lapatinib and/or capecitabine. End-points were response rate (RR), progression free survival (PFS), overall survival (OS) and toxicity.

Results: The overall response rate (ORR) was 33.3% (7/21) and all were partial response. For patients receiving prior WBRT and patients receiving LC as first line treatment for BCBM the ORR was 31.2% (5/16) and 40.0% (2/5) respectively. Median PFS was 5.5 months. Median OS was 11 months. Treatment-related adverse events were manageable. Grade 3–4 toxicities were hand-foot syndrome (14.3%), diarrhea (14.3%), nausea/vomiting (9.5%), mucositis (4.8%), and skin rash (4.8%).

Conclusion: The combination of LC is active and well-tolerated treatment in patients with HER2 + ve BCBM.

Introduction

Worldwide, breast cancer is the most common malignancy and cause of cancer-related death in women [1,2].

Breast cancer with brain metastases are the second most frequent secondary CNS metastases being only pre ceded by

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lung cancer [3]. Its incidence is strongly influenced by the biology of the primary tumor subtype, reaching its highest incidence in HER2-positive and TNBC subtypes and lowest in the luminal subtypes [4].

Treatment options for patients with brain metastases include surgery, stereotactic radiosurgery, whole-brain radiotherapy and steroids [5,6]. The development of effective systemic therapy for recurrent or progressed brain metastases after local treatment remains a major challenge and an urgent medical need [7].

The pattern of disease recurrence in the HER2-positive BC subtype has changed dramatically as a result of the routine use of adjuvant HER2-directed therapy. The use of adjuvant trastuzumab (Herceptin), has not only been effective in reducing the recurrence rates of HER2-positive breast cancer, but it has also altered the pattern of relapse and survival following the diagnosis of BCBM [8,9]. Interestingly, about half of patients treated with trastuzumab will either be responding to therapy or have stable disease at the time of diagnosis of BCBM; the remainder will die of progressive CNS disease [10]. While trastuzumab is relatively effective in visceral and bony disease, the brain is increasingly recognized as a sanctuary site for tumor cells due to the relative difficulty larger monoclonal antibody therapies have in penetrating the blood brain barrier (BBB) [10,11]. Evidence for this comes from the significantly lower cerebrospinal fluid levels of trastuzumab relative to plasma levels [12,13]. Interestingly, the CSF-to-serum trastuzumab concentration ratio has been shown to be improved in the setting of meningeal disease and WBRT [12].

Lapatinib which is a small molecule, has the ability to cross the BBB and acts as a reversible inhibitor of the intracellular tyrosine kinase domain of two members of the HER family, HER1 (EGFR-1) and HER2 (EGFR-2) through binding to the cytoplasmic ATP-binding site of the kinase and blocks receptor phosphorylation and activation, thereby preventing subsequent downstream signaling events [1,10,14].

Lapatinib markedly decreased thymidylate synthase (TS) expression, thus allowing capecitabine for better inhibition of the remaining enzyme activity. Additionally, it was suggested that concomitant administration is more likely to ensure better efficacy, as compared with sequential use [15].

On the basis of this evidence, we initiated this study to investigate tolerability and efficacy of the combination of LC in HER-2 positive BCBM.

Patients and methods

Patient eligibility criteria

Between January 2011 and January 2013, 21 patients with brain metastases HER2-positive BC in the Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital were included. Sixteen patients (76.19%) progressed after WBRT and 5 patients (23.81%) were treatment-naïve for brain metastases. Brain metastases were confirmed by computed tomography scan or magnetic resonance imaging with at least one measurable brain lesion of a size of 10 mm or greater in diameter. All patients received prior treatment with trastuzumab either in the adjuvant setting or for the metastatic disease.

Patients fulfilled the following criteria: age between 18 and 70 years with HER2 + ve (defined as 3 + immunohistochemistry or evidence of gene amplification by fluorescence in situ hybridization) BC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of $\leqslant 2$, adequate bone marrow reserve (WBC count $\geqslant 3.5 \times 10^9$/L, absolute neutrophil count of $\geqslant 1.5 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, and hemoglobin $\geqslant 10$ gm/dL), adequate renal function (measured creatinine clearance $\geqslant 60$ mL/min) and adequate liver function (transaminases less than $2 \times$ upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL).

Patients suffering from secondary malignancy or concurrent serious, uncontrolled medical illness (e.g. persistent immune-compromised states, uncontrolled infection, severe peripheral neuropathy, and clinically significant cardiac disease) were excluded from this study. Also patients with prior exposure to lapatinib or capecitabine, malabsorption or other gastrointestinal disease affecting absorption of oral medications, pregnancy or lactation and male sex were excluded.

All radiotherapy, chemotherapy, hormonal therapy, and/or trastuzumab had to be discontinued at least 2 weeks before initiation of protocol treatment. Concomitant bisphosphonates, mannitol, and corticosteroids were allowed, provided that the corticosteroid dose was stable for at least 1 week before inclusion.

Design of the study

This study is a prospective single-arm phase II single institution study. The Ethics Committee in the Faculty of Medicine, Tanta University, granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

Treatment plan and dose medication

Patients received lapatinib 1250 mg once daily every morning continuously and capecitabine 2000 mg/m^2/day, divided into two doses, on days 1–14, every 21 days.

Cycles were administered on an outpatient basis. Adequate hematological and within normal range organ functions were insured prior to each cycle. Chemotherapy was discontinued in case of disease progression or major toxicities.

Adverse events were monitored throughout the study. A complete resolution of hematologic and non-hematologic toxicity was required except for alopecia and fatigue. If toxicities did not resolve, then a 1-week delay was allowed.

Patient assessment

Assessment of clinical benefit

A tumor response assessment was performed after every three cycles of treatment. Pre- and on-treatment monitoring consisted of medical history, physical and neurological examination, CT-scan of the chest, abdomen and pelvis, and MRI or CT scan of the brain. Criteria of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were based on the standard definitions according to RECIST 1.0 criteria [16], with the overall response rate, including complete response and partial response. Progression of non-measurable CNS lesions, tumor-related increase in steroid dose, new or worsening tumor-related symptoms were considered as disease progression.