Original Study

Phase I Study of Panobinostat (LBH589) and Letrozole in Postmenopausal Metastatic Breast Cancer Patients

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Abstract

Epigenetic changes are important in cancer pathogenesis. In a phase I study of histone deacetylase inhibitor, we tested panobinostat combined with letrozole for safety and efficacy in patients with metastatic breast cancer. Our results have shown this combination is safe. The recommended dose for the phase II study was panobinostat 20 mg orally 3 times each week and oral letrozole 2.5 mg daily.

Introduction: Histone deacetylase inhibitors have been found to restore sensitivity to the estrogen receptor in endocrine-resistant and triple-negative breast cancer cell lines. We decided to test panobinostat, a pan-histone deacetylase inhibitor, because of preclinical data, combined with letrozole in a phase I study. **Patients and Methods:** We enrolled patients with metastatic breast cancer to determine the safety and tumor response using Response Evaluation Criteria In Solid Tumors. Dose level 1 was panobinostat 20 mg orally 3 times weekly with oral letrozole 2.5 mg daily. Dose level 2 was panobinostat 30 mg orally 3 times weekly, with the same dose of letrozole. **Results:** A total of 12 patients (6 at each dose level) were enrolled, and 43 cycles of treatment were given. Of the 6 patients at dose level 1, 1 experienced dose-limiting toxicity (20-mg dose level; an increase in creatinine). At the 30-mg dose level, 3 of 6 patients experienced dose-limiting toxicity, 1 each of grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia, and grade 3 diarrhea. The maximum tolerated dose was 20 mg. Of the 12 patients, 2 experienced a partial response, and 5 had stable disease. The most common severe adverse event was thrombocytopenia, occurring in 4 of 12 patients. **Conclusion:** The recommended phase II starting dose is panobinostat 20 mg orally 3 times weekly (eg, Monday, Wednesday, Friday) and oral letrozole 2.5 mg daily. This dose should be escalated to 30 mg orally 3 times weekly if no grade 3 toxicity has developed, because the partial responses occurred in patients receiving the 30-mg dose.

Clinical Breast Cancer, Vol. 16, No. 2, 82-6
Keywords: Aromatase refractory, Endocrine resistant breast cancer, Histone deacetylase inhibitors, Phase I study

Introduction

Changes in chromosome structure by epigenetic alterations play critical roles in the control of gene transcription. These epigenetic alterations include modification of histones and other proteins by acetylation and/or phosphorylation.[1,2] Normally, these modifications are finely balanced and are highly reversible in normal tissues; however, they can be imbalanced and heritable in tumor cells. Histone deacetylase inhibitors (HDACis) increase histone acetylation, thereby modulating the expression of a subset of genes in a coordinated fashion. Tumor suppressor genes are noted to be repressed by epigenetic mechanisms in several cancers.[3,4] Thus, therapy with HDACis can alter the tumor phenotype and inhibit tumor growth.[5] Additionally, breast cancer cell lines that were estrogen resistant or triple negative responded to an aromatase inhibitor (AI) or tamoxifen after pretreatment with an HDACi.[6,7] Panobinostat had been found to be a powerful pan-HDACi in preclinical studies when combined with letrozole. Thus, we

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Submitted: May 13, 2015; Accepted: Nov 10, 2015; Epub: Nov 17, 2015

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1526-8209/$ - see frontmatter
http://dx.doi.org/10.1016/j.clbc.2015.11.003

embarked on a phase I clinical trial that evaluated the safety and tolerability of panobinostat and letrozole in patients with metastatic breast cancer (MBC).

Patients and Methods

The Mayo Clinic institutional review board approved the study, and the trial was registered with ClinicalTrials.gov (clinicaltrials.gov identifier, NCT01105312). Patients were eligible to participate in the present study if they had met the following criteria: histologic proof of breast cancer that was metastatic at registration; evidence of MBC confirmed by radiologic imaging; measurable or nonmeasurable (evaluable) disease; postmenopausal; any receptor status, estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2) level; with or without previous treatment; and Eastern Cooperative Oncology Group performance status of 0 to 2. The reasons for excluding study participation included uncontrolled intercurrent illness; chemotherapy or radiation therapy 4 weeks before registration; radiation to $>$ 25% of the bone marrow; reversible effects of previous therapy; known central nervous system metastases or seizure disorder; and concurrent use of CYP3A4 inhibitors. Dose level 1 was panobinostat 20 mg orally 3 times weekly (Monday, Wednesday, Friday) with oral letrozole 2.5 mg daily. Dose level 2 was panobinostat 30 mg orally 3 times weekly with oral letrozole 2.5 mg daily.

A patient was deemed to have had a dose-limiting toxicity (DLT) if they had any of the following adverse events (AEs) in the first cycle of treatment that was deemed at least possibly related to study treatment: grade 3 electrocardiogram QT-corrected interval prolonged; grade 4 thrombocytopenia (or grade 3 thrombocytopenia with bleeding); grade 4 neutropenia (for $\geq$ 5 days); grade 4 anemia; febrile neutropenia; grade 3 nausea, vomiting, or diarrhea that did not responded to conventional therapy; any other grade 3+ nonhematologic event; creatinine increased $\geq$ 2 times from baseline; and any cardiac arrhythmia requiring new cardiac medication and/or hospitalization.

The primary endpoint of the present study was to determine the maximum tolerated dose (MTD) of panobinostat combined with letrozole. The MTD was defined as the highest dose that led to $<$ 2 DLTs (of 6 possible). The single secondary endpoint for the present phase I study was the tumor response determined using Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1.

Results

A total of 12 patients (6 at dose level 1 and 6 at dose level 2) were enrolled. Of the 12 patients, 10 had ER^+ disease and 2 had triple-negative breast cancer. Also, 6 had endocrine-resistant disease, 5 had experienced progression with AI therapy, and 4 had undergone previous treatment. Of the 12 patients, 6 had received $\geq$ 1 previous chemotherapy regimen and $\geq$ 1 hormonal therapy regimen, 4 had received 1 to 10 chemotherapy regimens, and 2 had received no previous chemotherapy or hormonal therapy. None of the patients had received hormonal treatment consisting of letrozole alone, and 1 patient had received tamoxifen, an AI, and fulvestrant. The baseline patient characteristics are listed in Table 1.

Table 1 Baseline Patient Characteristics (n = 12)

Characteristic	Value
Age (years)	
Median	63.5
Range	43-75
Female gender	12 (100)
Performance score	
0	10 (83)
1	2 (17)
Histologic type	
Infiltrating ductal	8 (67)
Infiltrating lobular	4 (33)
Metastases[a] (n)	
Median	2.5
Range	1-5
Previous therapies	
None	2
Chemotherapy and hormone therapy	6
Chemotherapy	4
Hormone therapy alone	0

[a]The most common were bone (n = 10), nodal-axillary (n = 5), nonaxillary nodal (n = 4), lung (n = 4), liver (n = 3), and chest wall (n = 3).

A total of 43 cycles of treatment were given. The initial cohort of 3 patients at the 20-mg dose level experienced no DLT. At the subsequent 30-mg dose level, 3 patients developed DLT (2 patients with thrombocytopenia, 1 grade 3 with bleeding, 1 with grade 4, and 1 with grade 3 diarrhea). In the subsequent cohort of 3 patients at the 20-mg dose level, 1 developed a DLT that manifested as an increase in creatinine. The most common severe AEs in the present study were thrombocytopenia (4 of 12) and neutropenia and hyponatremia (both in 3 of 12).

Of the 12 patients, 8 had measureable disease and 4 had evaluable disease only. Of the 8 patients with measurable disease, 2 had a partial response (endocrine-resistant and chemotherapy-resistant and treated at the 30-mg dose level) and 1 had stable disease (triple-negative and chemotherapy-resistant). One of these patients had a confirmed partial response and continued with the study drug for 6 cycles of treatment at the 30-mg dose (time to progression was 5.1 months). This patient experienced a DLT (grade 3 diarrhea) and also grade 3 anorexia. The remaining 5 patients with measurable disease had experienced progression at their first evaluation. The second patient with a partial response was also at the 30-mg dose level.

Of the 4 patients with stable disease, 3 were at the 20-mg and 1 was at the 30-mg dose level. A patient-by-patient listing of disease characteristics versus outcomes is presented in Table 2.

Of the 4 patients with evaluable disease, all had ER^+ and endocrine- and chemotherapy-resistant disease. All 4 had stable disease for a median duration of 5.6 months (range, 3.9-9.2 months). All these patients withdrew from the study without progression because of refusal, an AE, or the decision to start new treatment with another agent. None of the evaluable disease patients experienced a DLT; however, 1 experienced grade 3 thrombocytopenia and grade 3 neutropenia, another experienced grade 3 hypocalcemia, grade 3 hyponatremia, and grade 3 bladder infection, and 1 experienced grade 3 hyponatremia. Additional AE data, by