Apatinib in the treatment of HER-2 negative advanced breast cancer with chest wall metastasis：Multicenter Phase II clinical trial

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Introduction

Tumor metastasis is responsible for most of cancer deaths. Once diagnosed of breast cancer (BC), 25-50% of patients will eventually have metastasis in subsequent years. The mechanism of metastasis is a complex, multistep biological process, involving a multitude of genes, angiogenesis and biomolecules. Different molecular subtypes tend to have different initial metastatic sites. For instance, BC with HER2-positive to liver, triple-negative to lung and hormonal receptor positive (HR+) to bone were most common. However, despite of subtype, the rate of chest wall and lymph node metastasis is higher in all molecular subgroups. Recently, Song et al found that neutrophil extracellular traps (NETs) are abundant in the liver metastases of patients with breast and colon cancers, and that serum NETs can predict the occurrence of liver metastases in patients with early-stage BC. This indicates that studying organ specificity of tumor metastasis may also allow us to understand tumor behavior and lead to improvement of our therapeutic approach.

Angiogenesis serves an important role in tumor growth, invasion and metastasis in BC, while vascular endothelial growth factor (VEGF) and its receptors, specifically VEGF receptor 2 (VEGFR2), are predominantly responsible for angiogenic signaling. Bevacizumab (BEV) is a monoclonal antibody that binds to VEGF and inhibits the development of tumor vasculature, which has been proven to significantly increase progression free survival (PFS) when added to first line chemotherapy in MBC. VEGF-tyrosine kinases inhibitors (VEGF-TKIs) such as sunitinib and sorafenib have shown potential anti-tumor efficacy in MBC when combined with chemotherapies.

Apatinib is also an oral TKI that selectively inhibits VEGFR-2, inhibiting tumor angiogenesis, and has reported activity in BC. However, as BC with a chest wall metastasis (CWM) has rich vascular distribution, whether apatinib is also effective for BC with a CWM remains unknown. Precision treatment usually refers to treatment based on molecular markers. Therefore, in current clinical trial designs, organ specificity or organs are usually not the main consideration. Nevertheless, in our clinical practice, we found that type of organ metastasis was difference among molecular subtype. Patients with CWM may have more VEGFR expression, and rich neovascularization, which could have a better response to angiogenesis inhibitors. We found that the using of BEV or apatinib can rapidly shrink the mass in the chest wall, especially when the tumor is filled with rich blood vessels. Therefore, we designed this clinical trial, based on the characteristics of organs. To the best of our knowledge, this is the first study to assess the efficacy and safety of apatinib in HER-2 negative advanced breast cancer (ABC) with a CWM based on organ specificity.

Material and Methods

Patients and eligibility criteria

Inclusion criteria included women (≥18 years of age) with HER-2 negative ABC with CWM confirmed by histology or cytological examination, underwent first line chemotherapy regimen or cannot tolerate standard first-line treatment, having Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, having at least one measurable site of disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria that has not been previously irradiated. All patients had adequate hematologic, coagulation, hepatic, renal, and cardiac function, and had provided written, informed consent.

Patients were excluded for the following additional reasons: radiotherapy within 28 days before enrollment (radiotherapy to relieve metastatic bone pain before enrollment is permitted, but the irradiated medullary bone shall not exceed 30% of the total amount); symptomatic metastatic carcinoma to central nervous system; other carcinomas within 5 years; uncontrolled hypertension with antihypertensive therapy; ischemia of the myocardium (≥grade 2) or myocardial infarction, arrhythmia (≥grade 2, QTcF> 470 ms); grade III-IV cardiac insufficiency according to NYHA standard, or left ventricular ejection fraction (LVEF) < 50%; gastrointestinal disorder or other factors(dysphagia, chronic diarrhea or intestinal obstruction) that could interfere with drug absorption.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki, guidelines of the International Conference for Harmonisation/ Good Clinical Practice. This study was approved by the Ethics Committee of Beijing Cancer Hospital. Written informed consent was provided from all patients (2016YJZ19-GZ01). This trial was registered with ClinicalTrials.gov (NCT02878057).

Drug administration

Initially, all patients received apatinib 500 mg/d as the starting dose, and once a day (qd) 4 weeks as one cycle. Apatinib was administered until disease progression, death, consent withdrawal, unacceptable toxicity after 50% dose of reductions. Besides apatinib, patients with HR+ were given endocrine therapy (ET) at the same time. Apatinib was partially provided by the sponsor, Jiangsu HengRui Medicine Co., Ltd.

Apatinib dose will be allowed to reduce to 250 mg/d if patients experience the following conditions: grade 3/4 of hypertension, nausea, vomiting, proteinuria and diarrhea; grade 4 hematologic adverse events (AEs); other grade 3/4 non-hematologic AEs when investigators

considered dose reduction necessary.

Study design and assessments

This was an open-label, single-arm, phase II study conducted at four centers in China. The primary end point was progression free survival (PFS), defined as time from the date of enrollment (first-dosing) to first documented tumor progression or death of any cause, whichever occurred first.

Secondary end points included objective response rate (ORR), overall survival (OS), disease control rate (DCR), safety and tolerability. ORR was defined as the proportion of eligible patients who achieved a confirmed CR or PR by RECIST 1.1 criteria evaluated by the investigators. OS was defined as time from the date of enrollment to the date of death of any cause or the last follow-up visit. DCR was defined as the proportion of patients who achieved CR, PR and SD for at least 8 weeks. Patients eligible were evaluated by CT or MRI scan at baseline and every 2 cycles (8 weeks) thereafter until disease progression. Follow-up was done every 2 months until death or end of study.

AEs were assessed and graded according to the US National Cancer Institute Common Terminology Criteria for AEs (CTCAE), version 4.03. The safety evaluation was continued until 28 days after the last dose or recovery to grade 1 or 0 from any acute toxicities associated with apatinib.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0 (IBM, Chicago, IL). Median PFS (mPFS) were calculated using the Kaplan–Meier method. Safety data were summarized descriptively using data from all patients who received at least 1 dose of study treatment and had at least 1 post-baseline safety evaluation.

PFS and OS for patents who had at least 8 weeks treatment of apatinib were estimated using Kaplan–Meier method (unless progression during 8 weeks). Log-rank tests and Cox regression models were used for univariate and multivariate survival analysis of prognostic factors, and $p < 0.05$ was considered statistically significant.