Efficacy and Safety of High Dose Tamoxifen to Advanced Hormone Receptor-High Expressed Endocrine Therapy Resisted Breast Cancer: A Single-arm Phase II Pilot Trial

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Protocol Synopsis: This study conducted a single arm open label phase 2 trail. Patients received treatments of 100 mg/d tamoxifen. The primary endpoint was the progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR), overall survival (OS) and safety. Exploratory endpoints included the efficacy predictive value of the 18F-FES SUVmax.

Inclusion Criteria:

Eligible patients were 18-70 years old females with pathologically or histologically confirmed MBC and high expression of ER or progesterone receptor in metastatic or primary tumor lesions (immunohistochemical staining: ER-positive cells $\geq$ 60% and/or progesterone receptor-positive cells $\geq$ 60%). Patients had disease that progressed $\geq$ 12 months after adjuvant endocrine treatment or after receiving standard endocrine salvage treatment. Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. MBC had to be measurable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or had to be immeasurable bone-only disease. For patients who planned to undergo baseline 18F-FES PET/CT examination, discontinuation of TAM for $\geq$ 2 months was required to avoid the blockade of the imaging agent.

Exclusion Criteria:

The exclusion criteria included primary ET resistance (disease relapsed within the first 2 years of neoadjuvant or adjuvant ET or progressed within the first 6 months of ET for MBC); visceral crisis; evidence or history of central nervous system metastasis.

Interventions

After enrollment and the signing of informed consent, patients received oral 100 mg/d TAM treatment until disease progression.

Study Endpoints:

The primary endpoint was progression-free survival (PFS). The key secondary endpoints included ORR (the proportion of patients with complete response [CR] or partial response [PR] per RECIST version 1.1), CBR (the proportion of patients with CR, PR or stable disease [SD] $\geq$ 6 months), overall survival (OS), safety and tolerability. The exploratory endpoints included the predictive value of the 18F-FES maximum standardized uptake value (SUVmax) of 18F-FES PET/CT on the efficacy of high-dose TAM therapy.

Response evaluation criteria for a single lesion: referring to the RECIST 1.1 standard, we defined the response evaluation criteria for a single lesion. Progressive disease (PD): the maximum diameter of a single metastasis lesion increased by more than 20%; CR: disappearance of target lesions; PR: the maximum diameter of the lesion decreased by more than 30%; the rest were considered SD. The definition of clinical benefit of a single lesion: according to the response evaluation criteria for a single lesion, CR, PR, or SD $\geq$ 6 months was defined as clinical benefit of a single lesion.

Statistical Analysis

The primary endpoint of PFS was determined based on an intention-to-treat set. If no PFS event was observed before the cutoff date, the last tumor assessment date was defined as censored. Safety was analyzed based on a safety analysis set defined as all patients who received at least one dose of high-dose TAM and had at least one posttreatment safety assessment. Median PFS was estimated with the Kaplan-Meier method and compared by log-rank tests. The comparison of continuous variables between two samples of normal distribution was performed by the t-test, and the comparison of the two categorical data was conducted with the Chi-square test.

For all analyses, a 2-tailed $p \leqslant 0.05$ was considered statistically significant, and all confidence intervals used a 95% confidence level. Statistical analyses were performed by the investigators at the Cancer Center of Sun Yat-sen University using SPSS software version 20.0 (SPSS Inc.) and SAS version 9.4 (SAS Institute).