Effect of Capecitabine as Maintenance Therapy versus observation on patients with early stage triple negative breast cancer

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Introduction

The poor prognosis of triple-negative breast cancer (TNBC) results from a lack of available targeted treatment options coupled with the aggressive biological behavior of this subtype, which is associated with a high risk of early recurrence, particularly visceral metastasis.1,2 However, chemotherapy is the only adjuvant treatment option for patients with early-stage TNBC. Effective maintenance therapies to reduce the risk of relapse and death are needed.

Chemotherapy using lower dosage and higher frequency is thought to exert its anticancer activity by targeting 2 mechanisms of metastasis: angiogenesis and immune escape.3 Therefore, low-dose chemotherapy might prevent TNBC from metastasizing.

Capecitabine, an orally administered chemotherapeutic drug used widely in the treatment of metastatic breast cancer, is a potential candidate therapy for low-dose administration as maintenance to prevent recurrence.4-6

Several previous clinical trials added high-dose capecitabine to standard breast cancer adjuvant chemotherapy regimens and have reported conflicting results,7-11 In this study, was designed to evaluate the effect of low-dose capecitabine maintenance therapy after completion of standard adjuvant treatment on disease-free and overall survival in women with early-stage TNBC.

Aim of the work

The aim of work is to compare the efficacy and adverse events of low-dose capecitabine maintenance with observation following standard adjuvant treatment in patients with early-stage TNBC attend to oncology department, Beni- seuf university.

Study design

This study is a randomized, phase 2 clinical trial study and will be enrolled at clinical oncology department, Faculty of medicine, Beni-Suef University .

The study will investigate the effect of low dose and high frequency of receiving capecitabine as maintenance therapy in patients with low risk triple negative breast cancer.

Methods

Eligible patients will randomly open label assigned in a 1:1 ratio to receive either low-dose capecitabine maintenance (intervention group) which is newly diagnostic to be planned to receive capecitabine after finishing the standard adjuvant treatment or observation (control group) within 4 weeks after completion of standard adjuvant chemotherapy.

The capecitabine maintenance group will receive oral capecitabine at 650 mg/m2, twice daily continuously for 1 year.

Total follow up of the study is 2 years, one year for drug receving with monthy follow up for adverse effect and the other year for every 3 months follow up to asses DFS and OS.

Collection of capecitabine dose will receive and adverse events will assessed monthly during capecitabine maintenance in the capecitabine group. In both groups, physical examination, assessment of menopausal status, breast ultrasound, and abdominal ultrasound were performed every 3 months during 2 years of follow up; mammography and chest x-ray were performed yearly. Patients who has not experienced recurrence or death at the time of data analysis will censored as alive and event-free at the date of last follow-up.

Sample size

Sample size was calculated based on online openepi calculator. We calculated the required sample size to detect a statistically significant difference in AE rates between groups using a two-sided chi-square test. Therefore, our planned enrollment of 80 patients (40 per group) is sufficient to detect clinically meaningful differences in treatment-emergent adverse events.

Inclusion criteria

Eligible trial participants will women who has

1. Pathologically confirmed invasive breast ductal carcinoma

2. Hormone receptor negative (<1% positive cells by immunohistochemistry staining) and ERBB2 negative.

3. Participants had early-stage tumors that were stage T1b-3N0-3cM0, without positive supraclavicular or internal mammary lymph node involvement based on the American Joint Committee on Cancer (AJCC 2010, seventh edition) staging criteria.

4. They received standard treatments, including modified radical mastectomy or breast-conserving surgery, neo-/adjuvant chemotherapy, and radiotherapy according to institutional guidelines.

Exclusion criteria

Key exclusion criteria will include

1. Inflammatory or bilateral breast cancer.

2. History of invasive breast cancer or other malignancies; receipt of other biologic agents or immunotherapy.

3. Lactation or pregnancy; or severe coexisting illness.

Study end points

The primary end point of the study is to assess the adverse effects of the Capecitabine after 6 months after starting treatment.

Secondary end points will include

1. Disease-free survival, defined as the time from randomization to the first occurrence of the following events: local relapse, distant metastasis or contralateral breast cancer.

2. overall survival (the time from randomization to death from any cause).

3. Adverse events were assessed and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. Hand-foot syndrome (a common adverse effect of the fluoropyrimidine chemotherapy agent capecitabine) events will graded from 1 to 3.

Statistical Analysis:

For statistical analysis, all data will recorded and analyzed .The p-value reports will two tailed and an alpha level of 0.05 was used to assess statistical significance. Time-to-event curves will be described using the Kaplan-Meier method. A Cox proportional hazards model will be used to estimate and test the treatment effect. Analysis of the interaction between treatment effects and selected subgroups will conducted using a $\chi 2$ test for heterogeneity and described with forest plots. Q statistics and I2 values will be used to assess the potential heterogeneity of trial-specific Disease-Free Survival.The data will be coded and entered using: the statistical package for social science version 22 (SPSS v 22).For descriptive analysis of the result,the data will be summarized using (minimum, maximum, mean and standard deviation) for quantitative data and the frequency distribution for qualitative data.Student t- test: for comparison between means of two groups of quantitative variables.Paired sample t-test will be used for comparison between means of paired quantitative variables.Chi square test: for comparison between two groups of categorical data or frequency of events.

P: The probability/significance value

P value ≥ 0.05: Not significant

P value <0.05: Significant

The Correlation coefficient (r):A positive correlation coefficient means that as the value of one variable increases, the value of the other variable increases; as one decreases the other decreases. A negative correlation coefficient indicates that as one variable increases, the other decreases, and vice-versa.Graphic presentations in this study will done by: means of "Microsoft excel version 2007.

Ethical considerations:

This study will be approved by faculty of Medicine; Beni-Suef university research Ethics committee (FBBSU-REC)which adhered to principles of the Declaration of Helsinki. Informed consents will be signed from the participants, after explanation of the study to all participants.

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