Capecitabine in Combination with Aromatase Inhibitor Versus Aromatase Inhibitors, in Hormonal Receptor Positive Recurrent or Metastatic Breast Cancer Patients, Randomized Controlled Study (CONCEPT Trial)

Thesis

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List of Abbreviations

Abb.	Full term
5'-DFCR	5'-deoxy-5-fluorocytidine
5-FdUTP	Fluorodeoxyuridine triphosphate
5-FU	5-fluorouracil
5-FUDR	Floxuridine
ABC	Advanced breast cancer
AI	Aromatase inhibitor
AJCC	American Joint Committee on Cancer
ATR	Ataxia telangiectasia and Rad3-related
BMI	Body mass index
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
CAF	cyclophosphamide, Adriamycin and 5FU
CapAI	Capecitabine plus aromatase inhibitor
CBR	Clinical Benefit Rate
CDK 4/6	Cyclin-dependent kinase
CDK	Cyclin-dependent kinases
CI	Confidence interval
CMF	cyclophosphamide, methotrexate, and fluorouracil
COVID 19	Corona virus disease 2019
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
DDR	DNA damage response
DES	Diethyl stilbesterol
DFS	Disease-free survival
DNA	DNA deoxyribonucleic acid
DPD	dihydropyrimidine dehydrogenase

List of Abbreviations Cont...

Abb.	Full term
dThdPase	Thymidine phosphorylase
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
ET	Endocrine therapy
FDA	FDA food and drug administration
FdUMP	5-fluoro-2'-deoxyuridine monophosphate
FNA	Fine needle aspiration
FSH	follicular stimulating hormone
FUTP	5-fluorouridine triphosphate
G	Gap
GnRH	Gonadotropin-releasing hormone
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HR	Hormone receptor
HT	Trastuzumab, docetaxel
HTX	Trastuzumab, docetaxel and capecitabine
IDC	Invasive ductal carcinoma
IHC	Immunohistochemistry
LCIS	Lobular carcinoma in situ
LHRH	luteinizing hormone-releasing hormone
M	Mitosis
MBC	Metastatic breast cancer
MRI	Magnetic Resonance Imaging
NR	Not reached
NSAI	Non-steroidal aromatase inhibitor
ORR	Objective response rate
ORR	Overall response rate
OS	Overall survival
PF	phenylalanine mustard and 5-fluorouracil

List of Abbreviations Cont...

Abb.	Full term
PFS	Progression free survival
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PO	Per Os
PR	Progesterone receptor
PTEN	Phosphatase and tensin homolog.
QD	Quaque die (daily)
QOL	Quality of life
Rb	Retinoblastoma
RECIST	Response evaluation criteria in solid tumors
RNA	RNA ribonucleic acid
RR	Relative risk
S	Synthesis
SERM	Selective estrogen receptor modulator
T	Tamoxifen
TAM	Tamoxifen
TID	Ter in die (3 times a day)
TNM	Tumor, Node, Metastasis system
TP53	Tumour protein p53.
TS	Thymidylate synthase
TTF	Time to treatment failure
UK	United Kingdom.
US	Ultrasound
VEGF	Vascular endothelial growth factor

Abstract

Background: Combination therapies are becoming the new standard of care in treatment hormonal receptor (HR) positive human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer (ABC) patients. Most of the new drugs impose great financial burden especially in low-middle income countries. The need for studies to explore less expensive combinations is becoming crucial.

Patients and methods: In this prospective randomized phase II study: we randomly assigned 95 patients with HR positive, Her 2 negative ABC, who didn't receive previous systemic endocrinal treatment for advanced disease in both arms, to receive aromatase inhibitor (AI) or capecitabine (625 mg/m^2 bid PO for 14 days to be repeated every 21 days) plus AI administered daily. The primary endpoint was progression free survival (PFS) and secondary end point was toxicity.

Results: The median PFS was 18.7 months for the capecitabine plus AI (CapAI) arm versus 9.8 months for the AI only arm with a p value of 0.009 with a hazard ratio (HR) of 0.46 (95% CI 0.25-0.82).The median duration of follow up was 16.8 months (95% CI for the median; 14.1 to 17.9 months). The median number cycles of capecitabine received was was 12.3 cycles (range 0-38.4). Subgroup analysis revealed significant difference in favor of the CapAI arm for the premenopausal patients (p=0.04), visceral only and non-visceral only metastasis (p= 0.05, 0.04), non-oligometastatic patients (p=0.002) and patients who received treatment as first line (p= 0.02). Non-significant difference in PFS was found in the following subgroups; postmenopausal (p=0.05), bone only metastasis (p=0.22), oligometastatic (p=0.66), primary and secondary hormonal resistant patients (p=0.07, 0.07) and patients who received treatment beyond first line (p=0.32). There was no significant difference in the rates of toxicity in both arms regarding hematological toxicity (anemia, thrombocytopenia and neutropenia), fatigue, nausea, vomiting, diarrhea, mucositis. But there was significant difference in the hand foot syndrome (grade 1/2) with the 15.4% in the CapAI arm versus 0 % in the AI only arm, peripheral neuropathy (grade 1/2) with 23.1% vs 4.3% and hepatic toxicity (grade 1) 10.3% vs 0 %. Grade 3 toxicity was reported in only 3 patients in our study all in the CapAI arm (fatigue, thrombocytopenia and neutropenia). No permanent discontinuation occurred but 25% dose reduction was done in four patients due to decrease in creatinine clearance.

Conclusion: Among patients with HR positive Her2 negative ABC, combination of capecitabine with AIs showed significant improvement in median PFS than AI alone. With good tolerability and acceptable toxicity profile. Capecitabine AI combination might turn out to be the new standard of care for treatment of MBC patients. We recommend further studies with larger number of patients to be done evaluating combination therapy as first and second line treatment for ABC. ClinicalTrials.gov number NCT04012918

Keywords: breast cancer – chemo-endocrine- AI/Capecitabine

1. INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women worldwide, accounting for 25% of total cancer cases ***(Globocan, 2019).*** It is considered the most prevalent cancer among women in the Middle East and Northern Africa ***(Ferlay et al., 2015).*** In Egypt, breast cancer is the most common type of cancer among females ***(Ibrahim et al., 2014).***

Survival of breast cancer patients depends on the disease stage. Most of the patients with localized disease experience long-term disease-free survival. Meanwhile, those who develop metastasis have a 5-year relative survival of only 24% ***(Siegel et al., 2015).*** Hormone receptor (HR) positive represent the most common subset (almost 70%) in both early and advanced disease ***(Clarke et al., 2012).***

It is crucial to determine the menopausal status before initiation of treatment. For HR +ve / Human Human epidermal growth factor receptor 2 (Her 2) negative metastatic breast cancer patients who are premenopausal; If the patient had disease free survival (DFS) of 12 months or more, or if she was diagnosed with metastasis de novo, the recommended first line was either ovarian ablation plus tamoxifen or aromatase inhibitor ***(Cardoso et al., 2017).*** Aromatase inhibitors (AIs) are recommended for postmenopausal patients as their median progression-free survival (PFS) is between 8 and 10 months ***(Bonneterre et al., 2000).***

Chemotherapy regimens that are prescribed in HR positive metastatic breast cancer (MBC) patients include microtubule inhibitors (including taxanes and vinca alkaloids), anthracyclines, gemcitabine, cyclophosphamide and capecitabine. But endocrinal therapy is preferred as long as the patient is not in visceral crisis ***(Cardoso et al., 2017).***

Recently new drugs that increased progression free survival (PFS) has been approved in the treatment of HR positive metastatic breast cancer (MBC) as fulvastrant (Selective estrogen receptor modulator) ***(Ellis et al., 2015)*** and palbocilib (Ck4/6 inhibitor**)** as first line ***(Finn et al., 2015)*** and eveirolimus (mTor inhibitor) as second line ***(Pritchard et al., 2012).***

The optimum sequence of endocrinal treatment and chemotherapy has not been fully clarified, It is of great importance to bear in mind that the goal of treatment in recurrent and metastatic breast cancer is extending the progression free survival (PFS) and sustaining a good quality of life ***(Cardoso et al., 2017).***

A retrospective study by Shankar et al., that compared between combination of capecitabine and aromatase inhibitor (AI) versus capecitabine alone versus aromatase inhibitor alone showed that the median PFS of first-line treatment was significantly better for the combination with PFS 21 months vs 8 months for capecitabine and 15 months for AI. For second-line treatment, the PFS was longer in the combination

compared with capecitabine and AI groups (18 months vs. 5 months vs. 11 months, respectively) ***(Shankar et al., 2015).***

Alvarado et al., compared combination aromatase inhibitor plus capecitabine versus capecitabine alone versus aromatase inhibitor alone. The median PFS of first-line treatment was significantly better for the combination (PFS not-reached for combination vs. 3 months for capecitabine and 13 months for AI, $p<0.0001$). For second-line treatment, the PFS was longer in the combination compared to capecitabine and AI (PFS not reached vs. 6 months vs. 13 months, respectively, $p=0.041$) ***(Alvarado et al., 2012).***

In China a Phase II trial assessed the use of of metronomic oral capecitabine therapy combined with aromatase inhibitors in postmenopausal metastatic and recurrent breast cancer resistant to first-line AIs and the results showed overall response rate (ORR) 70.5% and median PFS 9.57 months ***(Jian-wei et al., 2015).*** Lee S. Schwartzberg conducted a phase II trial which results showed that fulvastrant with metronomic capecitabine for women with HR-positive, human epidermal growth factor receptor (HER2)-negative MBC had median PFS of 14.98 months ***(Schwartzberg et al., 2014).***

Capecitabine; being cheaper and more available in economically disadvantaged countries together with the promising results of the previous retrospective trial by Shankar et al and the prospective trial by Alvarado et al; further

confirmation of such results by a prospective randomized clinical trial is crucial. Currently a phase III trial under the title of "Metronomic Capecitabine Plus Aromatase Inhibitor for First Line Treatment in HR(+), Her2(-) Metastatic Breast Cancer" with the primary results expected to be published on 2021 ***(Sun Yat-sen University, 2016).***