A Retrospective Study Of the Efficacy And Toxicity Of Capecitabine In Advanced Breast Cancer

Thesis

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By

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Abstract

Maximum benefit is expected with careful selection of patients; young patients, those with good initial ECOG performance status, hormone receptor positive patients, chemotherapy-naïve patients, those with relatively low disease burden, and patients with no visceral sites of involvement.

Still, further larger multi-center studies are needed for proper characterization of our population, to identify prognostic factors and determinants of survival, and to maximize treatment strategies for our patients.

Keywords: Overall response rate - National Comprehensive Cancer Network - Myelocytomatosis oncogene - Immunoglobulin G - Gamma knife.

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Sarah Yousri Muhamad

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List of Abbreviations

Abb.	Full term

5-FU.....*5-fuorouracil*
AEs.....*Adverse events.*
AIs.....*Aromatase inhibitors.*
ASCO.....*American Society of Clinical Oncology.*
BCS.....*Breast conservative surgery.*
BID.....*Twice a day (bis in die).*
BMAs.....*Bone-modifying agents.*
BRCA.....*Breast cancer gene.*
CA.....*Cancer antigen.*
CBC.....*Complete blood count.*
CBR.....*Clinical benefit rate.*
CI.....*Confidence interval.*
CMF.....*Cyclophosphamide, methotrexate, fluorouracil.*
CNS.....*Central nervous system.*
CR.....*Complete response.*
CT.....*Computed tomography.*
CTCAE.....*Common Terminology Criteria for Adverse Events.*
DNA.....*Deoxy-nucleic acid.*
ECOG.....*Eastern Cooperative Oncology Group.*
EGFR.....*Epidermal growth factor receptor.*
ER.....*Estrogen receptor.*
FDA.....*U.S. Food and Drug Administration.*
FDG.....*Fluorodeoxyglucose.*
FGF.....*Fibroblast growth factor.*
GK.....*Gamma knife.*
HER.....*Human epidermal receptor.*
HFS.....*Hand-foot syndrome.*
HR.....*Hormonal receptor.*

List of Abbreviations (Cont...)

Abb.	Full term
IGF1	*Insulin growth factor 1.*
IgG	*Immunoglobulin G.*
ITT	*Intention to treat.*
LHRH	*Luteinizing hormone releasing hormone.*
mAb	*Monoclonal antibody.*
MABK	*Mitogen-activated protein kinase.*
MBC	*Metastatic breast cancer.*
MRI	*Magnetic resonance imaging.*
MRM	*Modified radical mastectomy.*
MSCC	*Metastatic spinal cord compression.*
mTORC1	*Mammalian target of rapamycin complex 1.*
MYC	*Myelocytomatosis oncogene.*
NCCN	*National Comprehensive Cancer Network.*
ORR	*Overall response rate.*
OS	*Overall survival.*
PD	*Progressive disease.*
PET	*Positron emission tomography.*
PFS	*Progression-free survival.*
PgR	*Progesterone receptor.*
PI3K	*Phosphatidylinositol-3-kinase.*
PLD	*Pegylated liposomal doxorubicin.*
PPi	*Inorganic pyrophosphate.*
PR	*Partial response.*
PS	*Performance status.*
RANK	*Receptor activator of nuclear factor kappa.*
Re-186	*Rhenium-186.*
RECIST	*Response Evaluation Criteria in Solid Tumors.*
RR	*Response rate.*
SD	*Stable disease.*

List of Abbreviations (Cont...)

Abb.	Full term
SERD	*Selective estrogen receptor degrader.*
SERM	*Selective estrogen receptor modulator.*
SLNB	*Sentinel lymph node biopsy.*
Sm-153	*Samarium-153.*
Sr-89	*Strontium-89.*
SREs	*Skeletal-related events.*
SRS	*Stereotactic radiosurgery.*
T-DM1	*Ado-trastuzumab emtansine.*
TNBC	*Triple negative breast cancer.*
TTF	*Time to treatment failure.*
TTP	*Time to progression.*
VEGF	*Vascular endothelial growth factor.*
Vs	*Versus.*
WBRT	*Whole-brain radiation therapy.*

INTRODUCTION

An estimated 6.7 million females were diagnosed with cancer worldwide in 2012. Breast cancer was the most common, accounting for a quarter (25%) of all cases diagnosed, with more than 1.5 million new breast cancer cases per year ***(Ferlay et al., 2012).***

Breast cancer was found to be the second leading cause of cancer death among women after lung cancer ***(DeSantis et al., 2013).***

About 20–40% of early breast cancer patients will go on to develop metastatic disease ***(Vera-Llonch et al., 2011).*** While approximately 5–10% of women already have metastatic breast cancer at diagnosis ***(Cardoso et al., 2012).***

Despite recent advances in formulating novel treatments, management of metastatic breast cancer (MBC) continues to be challenging, and MBC remains essentially an incurable disease ***(O'Shaughnessy, 2005).***

Treatment of MBC is individualized for each patient, and it is often based on patient's co-morbidities, performance status, prognostic factors, menopausal status, and prior history of treatments (including neoadjuvant or adjuvant treatments) and patient's preferences ***(O'Shaughnessy, 2005).***

The goals of treatment of MBC include disease control, palliation of symptoms, improving or maintaining quality of life, and prolonging overall survival ***(Chung et al., 2003).***

In 1998, a large multicenter, phase II trial tested the efficacy and safety of twice-daily oral capecitabine at 2,510 mg/m^2/d given for 2 weeks followed by a 1-week rest period and repeated in 3-week cycles, in patients with paclitaxel-refractory metastatic breast cancer. The overall response rate was 20% (95% confidence interval, 14%-28%). Median duration of response was 8.1 months, median survival time was 12.8 months, and the median time to disease progression was 93 days. The most common treatment-related adverse events were hand-foot syndrome, diarrhea, nausea, vomiting, and fatigue. Since then, Capecitabine is considered an active drug in the treatment of paclitaxel-refractory metastatic breast cancer. It has a favorable toxicity profile with the added advantage of being an oral drug administered at home ***(Blum et al., 1999).***

A randomized, open-label, phase II trial of oral capecitabine vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer was conducted between May 1996 and May 1997**.** The overall response rate in the capecitabine group was 30%, (95% confidence interval (95% CI), 19%-43%), including three complete responses (5%). The response rate observed in the CMF group was 16% (95% CI, 5%-33%) with no complete responses. Median time to disease progression was 41 months

with capecitabine and 30 months with CMF. Survival was similar in the two treatment groups (median 19.6 months with capecitabine, 17.2 months with CMF). The safety profiles were different for capecitabine and CMF. However, both regimens were generally well tolerated ***(O'Shaughnessy et al., 2001).***

O'Shaughnessy and colleagues conducted another trial comparing capecitabine (1250 mg/m2 twice a day for 2 weeks of every 3-week cycle plus docetaxel 75 mg/m2 on day 1) with docetaxel alone (100 mg/m2 on day 1) as first-, second- or third-line therapy for MBC. The activity of the combination was significantly greater, achieving a response rate of 42% compared with 30% in the docetaxel-alone arm ($p = 0.006$), and a 2-month increase in PFS ($p = 0.0001$). This translated into an absolute survival benefit of 3 months for the combination ($p = 0.0126$). Gastrointestinal side effects and hand-foot syndrome were more common with combination therapy, whereas myalgia, arthralgia, and neutropenic fever/sepsis were more common with single-agent docetaxel. More grade 3 adverse events occurred with combination therapy (71% *vs.* 49%, respectively), whereas grade 4 events were slightly more common with docetaxel (31% *vs.* 25% with combination). Despite the lower dose of docetaxel used in the combination arm. This confirmed the preclinical results with a demonstrable improvement in overall survival, and was one of the first trials to demonstrate a survival benefit of this extent in a combination chemotherapy regimen in advanced-stage breast cancer ***(O'Shaughnessy et al., 2002).***