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HER 2 NEU METASTATIC BREAST CANCER;

LOW DOSE SEQUENTIAL DOCETAXEL - CAPECITABINE CHEMOTHERAPY AS FIRST LINE TREATMENT. A CLINICAL TRIAL OF CANCER RESEARCH GROUP PAKISTAN

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ABSTRACT... Objective: To evaluate the efficacy and toxicity of low dose sequential docetaxel-capecitabine chemotherapy as first line treatment of HER 2 negative metastatic breast cancer (MBC). **Design:** Experimental Study, Clinical Trial. **Setting:** Three different oncology centers, collaborating under the Cancer Research Group Pakistan. **Period:** From June 2006 to December 2007. **Methods:** Female breast cancer patients with visceral or visceral and bone metastases and a KPS $\geq$ 70 were eligible. **Results:** 38 patients were enrolled. Median age was 49 years (Range 32-70). With docetaxel treatment, CR was seen in 06 (16%) patients and PR in 20 (53%) with an overall response rate of 69%. Stable disease was seen in 10 (26%) and PD in 02 (05%). Four out of six complete responses were in patients with liver metastases. Thirty six patients received capecitabine. Thirty were evaluable for response. Capecitabine added one CR (3.33%) and six partial responses (20%). Two patients (6.67 %) who had a partial response to docetaxel relapsed during capecitabine treatment. As a result at the completion of the therapy CR was seen in 07 patients (18.42%), PR in 23 patients (60.53%) with SD and PD in, 4 patients (10.53%) each. An overall RR of 78.94 % was seen. Median time to progression was 10.9 months (range, 3-22 months) and at a median follow up time of 24 months (range, 16 -34 months) 13 patients have died with an overall survival probability of docetaxel –capecitabine sequential therapy of 0.68. Significant docetaxel specific grade 3/4 toxicities included neutropenia and diarrhea in 14 (36.84%) and 03 (07.89%) respectively. Febrile neutropenia was seen in 06 (15.79%). Capecitabine specific significant grade 3 toxicities included hand-foot syndrome in three patients (8.33%) and diarrhea in 2 (5.56%). Stomatitis, dermatitis, fatigue was seen in one patient (2.78 %) each. **Conclusions:** This treatment schedule of low dose sequential docetaxel - capecitabine is an effective first line treatment of HER 2 negative MBC that provides good overall response rate, manageable toxicity and improved survival.

Key words: Capecitabine, Docetaxel, Metastatic Breast Cancer.

INTRODUCTION

Metastatic breast cancer is unlikely to be cured with hormone therapy, chemotherapy, targeted therapy, high dose chemotherapy and stem cell transplant or by any other means. Only a few percent of treated patients live beyond five years[1]. Therefore, the treatment objectives are the prolongation of survival and symptom control.

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These are best achieved by carefully selecting the treatment modalities based on the individual patient characteristics.

Slowly growing visceral disease or metastatic disease in bones and soft tissues is best treated with hormone therapy in hormone receptor positive patients. Rapidly progressive visceral disease or hormone refractory disease is best treated with chemotherapy. Transtuzumab is additionally incorporated in treatment of patients who over express HER 2 neu.

Docetaxel[2-4] and doxorubicin[5-8] are two most potent cytotoxic therapies used in metastatic breast cancer. These two most active drugs are generally not given in combination as they are associated with significant hematologic toxicity. Furthermore, combination chemotherapies may increase toxicity without increasing therapeutic effectiveness. Single agent therapies are preferred by many. Single agent sequential therapy may be associated with less treatment related toxicity and may improve the quality of life. Docetaxel, the more potent of the taxanes[3] is the usual first choice. Several studies have demonstrated the activity of capecitabine after docetaxel failure[9-11].

Therefore, the logical choice of a sequential therapy would be to use single agent capecitabine subsequent to single agent docetaxel. Although, the preclinical and clinical synergy of docetaxel and capecitabine has led to the use of this doublet up front in MBC with minimal benefit in progression free survival and overall survival, the toxicity has been significant in terms of diarrhea, stomatitis, and hand foot syndrome[12]. Another small study has compared this doublet of docetaxel plus capecitabine against the second line use of capecitabine after first line docetaxel and revealed better response rates, time to disease progression and overall survival[13]. Despite these studies the superiority of this doublet is not yet clearly established. There is no data on the comparison of this doublet against the sequential use of these two drugs. On the other hand in the O' Shaughnessy study patients who received second line capecitabine after docetaxel failure (>25%) had significantly grater survival rates then patients who received other types of chemotherapies[14].

Therefore, the role of sequential therapy is not yet fully defined. The best way to use docetaxel and capecitabine in MBC is not known. This study was conducted with the objectives to document the efficacy and toxicity of sequential single agent docetaxel followed by single agent capecitabine in a uniform patient population of HER 2 negative and rapidly progressive diseases.

MATERIAL & METHODS

This study was conducted in three different oncology centers, collaborating under the Cancer Research Group Pakistan. Eligibility criteria required evidence of metastatic disease on clinical and radiological basis in patients who previously had histologically or cytologically confirmed carcinoma of the breast. For single metastatic focus histological or cytological confirmation was required. Patients with rapidly progressive visceral metastasis or visceral and bone metastasis were eligible. Metastatic disease which could be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm with conventional techniques or as $\geq$ 10 mm with spiral CT scan was included. Hormone receptor negative patients and patients with hormone sensitive disease who progressed after first line hormone therapy for metastatic disease were considered eligible. Adequate hematological functions (ANC $\geq$ $2.0x10^9$/, platelets $\geq$ $100x\ 10^9$ /L), hemoglobin $\geq$ 10g/ dl and adequate hepatic functions with total serum bilirubin < 1 x upper normal limit, AST and/or ALT $\leq$ 1.5 x upper normal limit and alkaline phosphatase $\leq$ 2.5 x upper normal limit was required.

Adequate renal function with creatinine clearance greater than 51 ml/ minute normal LVEF at baseline and a KPS 60 or above was essential. Adult females between 18 to 70 years who volunteered a written informed consent with permission to contact them at their residential address during follow up were enrolled.

EXCLUSION CRITERIA

Patients with slowly progressive non visceral metastatic disease were excluded. Patients with HER 2 Neu-3+ on

Immunohistochemistry were also excluded. Patients with congestive heart failure or angina pectoris even if medically controlled and patients with uncontrolled hypertension or arrhythmia, prior history of myocardial infarction were also excluded. Patients with unstable peptic ulcer disease, uncontrolled diabetes mellitus or other contraindication for the use of corticosteroids were also excluded.

Eligible patients were given 75 mg/ m^2 of docetaxel (Donataxel: Biopropharma: supplied by Ferozsons Laboratories Limited Pakistan), as one hour intravenous infusion every 3 weeks for 4 consecutive cycles.

Patients with SD, PR or CR after four cycles were given capecitabine. Capecitabine was given at a dose of 1000 mg/ m^2 BID P O for 14 days, for four cycles repeated every 3 weeks. Patients with PD during docetaxel or capecitabine treatment were given gemcitabine or Vinorelbine chemotherapy.

Docetaxel treatment was delayed till a maximum of seven days for persistent myelotoxicity till the scheduled day, i.e ANC <15x10^9, platelets <100x10^9. Prophylactic use of colony stimulating factor was not allowed. One dose reduction of 20 % for docetaxel was permitted in subsequent cycle in case of grade III diarrhea, stomatitis, or skin reaction, grade IV neutropenia with grade I fever (febrile neutropenia). Febrile neutropenia was managed according to the IDSA Guidelines.

Capecitabine dose reduction was not allowed for grade 1 or 2 toxicities but a dose delay of one week was allowed for recovery from side effects. Twenty percent dose reduction for subsequent cycles was made in case of grade 3 hand foot syndrome or diarrhea. Grade 3 hand and foot syndrome was defined as moist desquamation, ulceration, blistering and severe pain of the hands and / or feet and /or severe discomfort rendering the patient unfit for daily work or activities.

Documentation of parameters of disease included hormone receptor status, HER 2 neu status of primary breast cancer, disease free interval and menopausal status. Hormone receptor and HER 2 neu status of metastatic disease was not determined. This was a phase II, multicenter, non-blinded, non-randomized prospective study. Response Evaluation Criteria in Solid Tumors (RECIST) was used for evaluation of response. Radiological response evaluation was done by an independent Radiologist. Responses were evaluated by the same investigation which was used initially for evaluation of the measurable disease. Overall survival and time to tumor progression were documented. Overall survival was calculated from the date of first dose of docetaxel –capecitabine sequential therapy till death due to any cause. Kaplan Meier product limit method was used for estimating survival. TTP was calculated from the date of first dose of docetaxel until progression.

Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 was used for evaluation of toxicity.

Acute toxicity was monitored before the start of each cycle and on day 10 of chemotherapy. Late toxicities were monitored during monthly follow-up visits.

Docetaxel-specific side effects including neutropenia, febrile neutropenia, diarrhea, arthralgia, neurosensory change, fluid retention syndrome (FRS), nail changes and capecitabine specific side effects including hand foot syndrome, diarrhea, dermatitis, and stomatitis were monitored vigilantly. Toxicities were evaluated in all patients who received one or more cycle of chemotherapy.

RESULTS

Patient characteristics and parameter of disease are given in table-I. With docetaxel treatment, CR was seen in 06 patients (16%) and PR in 20 patients (53%) with an overall response rate of 69%. Stable disease was seen in 10 patients (26%) and PD in 02 (05%). Four out of six complete responses were in patients with liver metastases. Thirty six patients received capecitabine. Thirty were evaluable for response. Capecitabine added one CR (3.33%) and six partial responses (20%). Two patients (6.67%) who had a partial response to docetaxel relapsed during capecitabine treatment. As a result at the

completion of the therapy CR was seen in 07 patients (18.42%), PR in 23 patients (60.53%) with SD and PD in 4 patients (10.53%) each. An overall RR of 78.94 % was seen. Response evaluation did not include bony sites of disease.

Table-I. Patients characteristics and parameter of disease.	
Median age	49 years
Range	32-70 years
Sites involved	
Visceral	10
Visceral plus bones or soft tissues	28
Menopausal status	
Pre menopausal	20
Post menopausal	18
Hormone receptor status	
ER/PR positive	16
ER/PR negative	22
Disease free survival	
Less then 2 years	16
More then 2 years	20

Median time to progression after completion of sequential therapy was 10.9 months (range, 3-22 months) and at a median follow up time of 24 months (range, 16 -34 months) 13 patients have died with an overall survival probability of docetaxel –capecitabine sequential therapy 0.68 (figure-1). Docetaxel specific side effects are given in table-II. Grade 3/4 toxicities included neutropenia in 14 (36.84%) and febrile neutropenia in 06 (15.79%). Diarrhea and fatigue in 03 (07.89%) patients each and grade 3/4 stomatitis in 01 (02.63%) patient.

Capecitabine specific side effects are given in table-III. Grade 3 hand-foot syndrome was seen in three patients (8.33%), diarrhea in 2 (5.56%), stomatitis, dermatitis, fatigue in one patient (2.78 %) each.

Fig-1. Kaplan Meier Survival Curve (N=38)

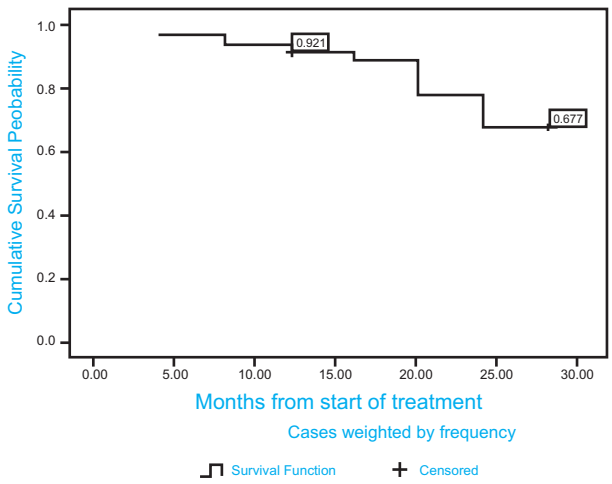

Table-II. Docetaxel Toxicity.		
Grade 2-3 Toxicity (n = 38)		
Toxicity	**Grade 2. No(%)**	**Grade 3/4. No (%)**
Neutropenia	22(57.89%)	14(36.84%)
Diarrhea	06(15.79%)	03(07.89%)
Stomatitis	04(10.53%)	01(02.63%)
Fatigue	08(21.05%)	03(07.89%)
Thrombocytopenia	02(05.26%)	02(05.26%)
Anaemia	14(36.84%)	02(05.26%)
Febrile neutropenia	06(15.79%)	

No other grade 3 or 4 hematological or non hematological toxicity was documented. Most common hematological toxicity included lymphopenia and anemia seen in 16 (44.44%) and 14 (38.89%) respectively.

DISCUSSION

There is no published data to date, on the sequential use of capecitabine given to docetaxel sensitive metastatic breast cancer patients in the first line setting. Similarly there is no data comparing the docetaxel capecitabine

Table-III. Capecitabine Toxicity.		
Grade 2-3 Toxicity (n = 36)		
Toxicity	**Grade 2. No(%)**	**Grade 3. No(%)**
Hand foot syndrome	12(33.33%)	03(8.33%)
Diarrhea	06(16.67%)	02(5.56%)
Dermatitis	06(06.67%)	01(2.78%)
Stomatitis	10(27.78%)	01(2.78%)
Fatigue	08(22.22%)	01(2.78%)
Nausea & vomiting	08(22.22%)	00(0.00%)
Lymphopenia	16(44.44%)	00(0.00%)
Neutropenia	08(22.22%)	00(0.00%)
Thrombocytopenia	02(05.56%)	00(0.00%)
Anaemia	14(38.89%)	00(0.00%)

doublet with the sequential use of docetaxel-capecitabine in first line treatment of metastatic breast cancer. Two studies have reported the use of this doublet in MBC[12,13]. In O'shaughnessy, study this doublet was compared to docetaxel monotherapy in a heterogeneous patient population of locally advanced and metastatic breast cancer patients who have already received upto 2 prior chemotherapies for advanced disease including paclitaxel therapy[12]. In the second study Beslija S et al compared the planned sequence of docetaxel followed at relapse by capecitabine with docetaxel doublet as first line treatment of MBC[13]. Capecitabine given as a second line therapy upon docetaxel failure cannot be considered as a sequential therapy. Therefore, the value of truly sequential docetaxel capecitabine treatment remains to be ascertained particularly in comparison to its concomitant use.

This small study focuses on the sequential use of capecitabine in patients who respond to docetaxel or become stable on docetaxel. Capecitabine added seven more responses including one CR and six partial responses. RECIST used in this study tended to underestimate the responsiveness of metastatic breast cancer to chemotherapy, as patients with complete disappearance of target lesions in the presence of persisting non target lesions were to be classified as partial responders according to RECIST. However, an overall response rate of 78.94 % is higher then that of 68 % seen with docetaxel capecitabine doublets in Beslija et al's study of first line therapy[13]. As clinical responses do not predict overall survival it is more important to measure time to tumor progression in this setting.

This sequence has yielded median time to tumor progression of 10.9 months and a 2 year survival probability of 0.68. No patient was denied subsequent chemotherapies. Gemcitabine was given in all and vinorelbine or others in most patients. The survival data of this study shall be interpreted in the light of established efficacy of these drugs in second line or third line setting.

A median survival of 14.5 months seen with the doublet of docetaxel plus capcitabine against 11.5 months with single agent docetaxel[12] is not directly comparable with this study however it emphasizes the need for a direct comparison of this sequential approach with concomitant therapy, as this approach offers minimal toxicity along with a reasonable survival advantage.

Neutropenia, and diarrhea are the most frequent grade 3 toxicities with docetaxel and hand foot syndrome, diarrhea and stomatitis are seen frequently with capecitabine. In principal combination chemotherapies should not have overlapping toxicities and as diarrhea is seen significantly with both the docetaxel and capecitabine, these two drugs shall not be combined. Despite this fact this doublet has been tried and has been approved for the treatment of metastatic breast cancer though it potentially carries the risk of fatalities due to life threatening diarrhea. Toxicity of this doublet often necessitates a dose reduction. A 50-75 % dose reduction of capecitabine was required in majority of patients in docetxel-capecitbine versus docetaxel trial. A retrospective analysis from M. D. Anderson Cancer Centre reported grade 3/4 hand foot syndrome, diarrhea, and stomatitis in 20%, 3%, 3% patients, respectively, with 28 % requiring dose modification at higher dosage level [15]. Whereas with sequential capecitabine at 2000 mg /m^2

toxicity is mild and dose modification is required for only few patients. In our study grade 3 hand-foot syndrome was seen only in 8% and diarrhea in 6%.

All the data supports the use of a reduced dose of capecitabine sequentially after 75 mg /m^2 docetaxel as it has a favorable toxicity profile while retaining reasonably high response rate and survival prolongation.

CONCLUSION

This treatment schedule of low dose sequential docetaxel-capecitabine is an effective first line treatment of HER 2 negative MBC with good overall response rate and manageable toxicity.

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Success is the ability to go from one failure to another with no loss of enthusiasm.

Sir Winston Churchill