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SINGLE AGENT LOW DOSE CAPECITABINE SUBSEQUENT TO DOCETAXEL CHEMOTHERAPY IN HER-2 NEGATIVE METASTATIC BREAST CANCER.

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ABSTRACT
The objective of this study was to evaluate the efficacy and toxicity of low dose capecitabine chemotherapy in patients with metastatic breast cancer (MBC) who have previously received first line docetaxel chemotherapy. Metastatic breast cancer patients who responded or achieved a stable disease with first line docetaxel were enrolled. Female patients with visceral or visceral and bone metastases and a KPS > 70 were eligible. Adequate marrow, renal and hepatic function was required. Metastatic brain disease and bone as the only site of disease were excluded. Informed consent was obtained from all patients. Capecitabine 1,000 mg/m² B.I.D 14 days for four cycles were given. Cycles were repeated every 3 weeks. Response Evaluation Criteria in Solid Tumors (RECIST) was used for evaluation of response and common Toxicity Criteria (CTC) Version 3.0 for evaluation of toxicity. From September 2006 to December 2007, 38 patients were enrolled. Median age was 49 years (Range 32-70). Thirty six patients had received docetaxel at a dose of 75 mg/m² for four cycles. Six patients had already achieved a complete response, 20 partial response and ten had achieved stable disease. Capecitabine added one CR (3.33%) and six partial responses (20 %). Median time to progression after capecitabine was 6.9 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 grade 3 toxicities included hand-foot syndrome in three patients (8.33%), diarrhea in 2 (5.56%), stomatitis, dermatitis, fatigue and decrease in appetite in one patient (2.78 %) each. Grade 2 toxicity included hand-foot syndrome in 12 (33.33%) patients, diarrhea and stomatitis in 8 patients (22.22%) each. Most common hematological toxicity included lymphopenia and anemia seen in 16 (44.44%) and 14 (38.89%) respectively. This treatment schedule of low dose capecitabine after docetaxel treatment is an effective treatment of MBC and has a manageable toxicity profile.

Key Words: *Capecitabine, Docetaxel, Metastatic breast cancer.*

INTRODUCTION

Due to the lack of a substantial survival difference and quality of life (QOL) benefit, therapy with single agents is generally considered a reasonable alternative to combination chemotherapy in treatment of MBC. On the other hand, combination chemotherapy is considered more appropriate in symptomatic patients or in those with rapidly progressive visceral metastases provided they have a good performance status.

For women with HER-2 negative MBC, chemotherapeutic options include the use of anthracyclines, taxanes, capecitabine, gemcitabine, or oral etoposide. Most patients receive taxanes or anthracyclines as first line treatment, and the choice for second line therapy is usually based on gemcitabine, capecitbine or vinorelbine. Capecitabine is an attarctive option because it has shown a consistent response rate of 20% in patients who have failed on first line docetaxel.[1-3]

Single agent chemotherapies can be given sequentially without treatment interruptions and without waiting for the disease to relapse or progress. Single agent sequential therapy is generally associated with less treatment related side effects and in fact may improve the quality of life. One such regimen of interest is docetaxel–capecitabine sequential chemotherapy. Irrespective of the setting in which capecitabine is used, the dose and schedule of this drug is constantly being re-defined.

Capecitabine is a 5-FU pro-drug that is absorbed intact through the intestinal wall and is then converted to 5-Fluorouracil in three sequential enzymatic reactions. The final reaction requires thymidine phosphorylase enzyme which is present at consistently higher levels in tumor as compared to normal tissues. This provides the basis for enhanced selectivity for tumor cells and better tolerability of this drug.

Approved dose of 2500 mg/m² daily for 14 of every 21 days is too high for our patients, who generally tolerate chemotherapies poorly. A very high frequency of dose limiting palmar-plantar erythrodysesthesia (hand-foot syndrome) is observed in

our population. However there is no local data to support this notion and the efficacy of lower doses is not well established. We have recently completed a study of sequential single agent docetaxel followed by single agent capecitabine in a uniform patient population with HER-2 negative rapidly progressive metastatic breast cancer. Here we are separately reporting the efficacy and toxicity of single agent low dose capecitabine in advanced breast cancer patients who have been pretreated with docetaxel.

MATERIAL AND METHODS

This study was performed at Clinical Oncology Department of King Edward Medical University / Mayo Hospital Lahore, Combined Military Hospital Lahore, and Jinnah Post Graduate Medical Center Karachi, from September 2006 to December 2007. Metastatic breast cancer patients who had previously received docetaxel as first line treatment were eligible provided they had achieved a stable disease, partial response or complete response. Thirty six patients had received docetaxel at a dose of 75 mg/ m^2 for four cycles. Six patients had already achieved a complete response, 20 partial response and ten had achieved stable disease. Two patients had PD and received only two cycle of docetaxel.

Adequate hematological functions with ANC $\geq 2.0\times10^9$/, platelets $\geq 100 \times 10^9$/L, hemoglobin $\geq$ 10g/dl and adequate hepatic functions with total serum bilirubin $< 1 \times$ upper normal limit, AST and/ or ALT $\leq 2.5 \times$ upper normal limit and alkaline phosphatase $\leq 2.5 \times$ upper normal limit were required.

Adequate renal function with creatinine clearance greater then 51 ml / minute and a KPS 60 or above was essential. Capecitabine (Xeloda, Roche Pakistan Limited) was given at a dose of 1000 mg / m^2 BID P O for 14 days, every 3 weeks for four cycles. Patients were instructed to take the tablets with water within 30 minutes after a meal. 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-foot syndrome was pre 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. All patients with PD and all relapsed patients were given gemcitabine subsequently.

Pre-study assessment included general physical examination, ECG, chest X-Ray postero-anterior view, CT scan of neck, chest, abdomen and pelvis and bone X-rays of involved areas. Documentation of parameters of disease included hormone receptor status, HER-2 neu status of primary breast cancer, record of measurable disease according to RECIST criteria, and menopausal status. Hormone receptor and HER-2 neu status of metastatic disease were not re-evaluated.

This was a phase II, multicenter, non-blinded, prospective study. Response Evaluation Criteria in Solid Tumors (RECIST) was used for evaluation of response. Common Toxicity Criteria (CTC) Version 3.0 was used for evaluation of toxicity. Toxicities were evaluated on all patients who have received one or more cycle of capecitabine.

Acute toxicity was monitored before the start of each cycle and on Day 14 of chemotherapy. Late toxicities were monitored during monthly follow-up visits.

Capecitabine specific side effects including hand foot syndrome, diarrhea, stomatitis and fatigue were monitored vigilantly. ECG was repeated every two cycles.

Responses were evaluated after every two cycles of chemotherapy with the same method of measurement as used at baseline. Radiological response evaluation was done by an independent radiologist.

Overall survival and time to tumor progression were documented. TTP was calculated from the date of first dose of docetaxel until disease progression. 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.

RESULTS

Thirty patients were evaluable for response and all thirty six were evaluable for toxicity. Capecitabine added one CR (3.33%) and six partial responses (20%) with an overall response rate of 23.33%. Two patients (5.56%) who had a partial response to docetaxel relapsed during capecitabine treatment. Partial responders had gross reduction or complete resolution of target lesions with the persistence of non target lesion.

Median time to progression after capecitabine was 6.9 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).

A total 140 treatment cycles were delivered with a median of 4 cycles. Dose was delayed for up to a week in 7 patients and 20% dose reduction was made in 5 (13.89%) patients. Complete toxicity profile is given in table 1. Grade 3 hand-foot syndrome was seen in three patients (8.33%), diarrhea in 2 (5.56%), stomatitis, dermatitis, fatigue and decrease in appetite in one patient (2.78%) each. Diarrhea typically occurred after second course of chemo-

Table 1: *Grade 2 – 3 Toxicity (N = 36).*

Toxicity	Grade 2 No. (%)	Grade 3 No. (%)
Hand foot syndrome	12 (33.33%)	03 (8.33%)
Diarrhea	08 (22.22%)	02 (5.56%)
Stomatitis	08 (22.22%)	01 (2.78%)
Dermatitis	06 (16.67%)	01 (2.78%)
Fatigue	08 (22.22%)	01 (2.78%)
Nusea and vomiting	08 (22.22%)	00 (0.00%)
Appetite decrease	06 (16.67%)	01 (2.78%)
Bilirubin increase	04 (11.11%)	00 (0.00%)
Edema	02 (05.56%)	00 (0.00%)
Eye irritation	01 (02.78%)	00 (0.00%)
Lymphopenia	16 (44.44%)	00 (0.00%)
Anaemia	14 (38.89%)	00 (0.00%)
Neutropenia	08 (22.22%)	00 (0.00%)
Thrombocytopenia	02 (05.56%)	00 (0.00%)

therapy. No other grade 3 or 4 hematological or non hematological toxicity was documented.

Grade 2 toxicity included hand-foot syndrome in 12 (33.33%) patients, diarrhea and stomatitis in 8 patients (22.22%) each. Nausea and vomiting in 8 (22.22%) and appetite decrease in 6 patients (16.67%). Dermatitis was seen in 6 patients (16.67%).

Most common hematological toxicity included lymphopenia and anemia seen in 16 (44.44%) and 14 (38.89%) respectively. Serial ECG's did not detect any change during or immediately after the treatment.

DISCUSSION

In general, response rates to initial therapy with taxanes, anthracyclines, gemcitabine, capecitabine and vinorelbine range from 25% to 60% and are reduced significantly with use of these drugs as second line treatment[4]. In sequential therapy the drugs used after the initial therapy do not typically constitute the second line setting as patients are still responding or sensitive to the first line treatment. Response rates in this setting do not have same meanings and therefore, the time to tumor progression and overall survival becomes more important outcome measure. However, a response rate of 23.33% in this study with sequential use of capecitabine adds importantly to the initial response rate to docetaxel therapy. A partial response in RECIST also includes complete resolution of tar- get lesions in the presence of persisting non target lesions. Therefore, RECIST tends to underestimate the

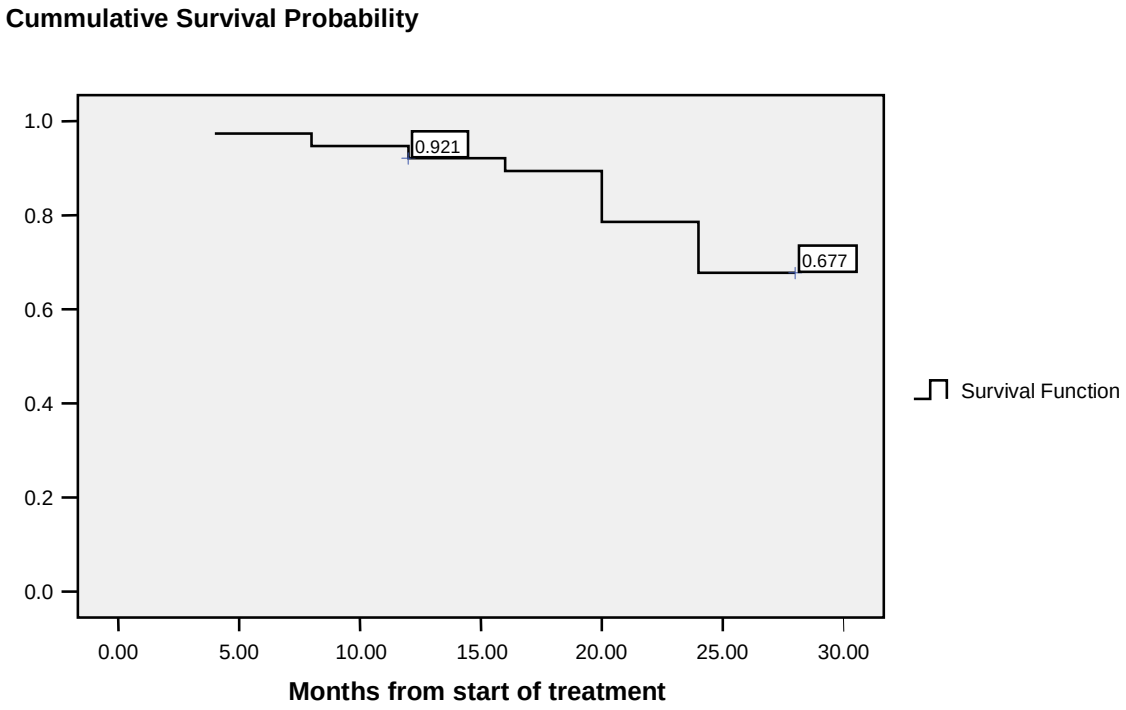

Figure 1: *Kaplan Meier Survival Curve. N = 38.*

responsiveness of metastatic breast cancer to chemotherapy.

This sequence of chemotherapies has yielded median time to tumor progression of 6.9 months and a 2 year survival probability of 0.68. Contribution of individual drugs given in sequence is difficult to be evaluated. But this is essentially similar to the outcomes obtained in most other reported series. What is of interest is the use of a different dose regimen of capecitabine then the recommended dose because of the concerns for toxicity in our patient population and therefore the tolerability and toxicities have been specifically described in this report.

Hand-foot syndrome and diarrhea are the two most common dose limiting toxicities of capecitabine. Capecitabine used in a similar setting but at a dose of 2500 mg/m²/day produces an overall hand foot syndrome in 62% patients including grade 3 in 22%.[1] In this study, at a dose of 2000 mg m²/day, 41.67 % patients had grade 2/3 hand foot syndrome with only 8.33% with grade 3 lesion. A small study on 24 patients has shown a similar toxicity with the reduced dose.[5] Patients with grade 3 hand foot syndrome are unable to walk and therefore their daily routines are disrupted. No specific treatment for reversal or prevention of this side effect exists and patients are generally offered bland creams and lotions for soothing effects. The only way to prevent this is to reduce the subsequent dose which minimizes the chances of severe symptoms.

Blum JL et al[1] in their study have reported 16% grade 3 diarrhea, whereas, we have seen it in only 5.56% cases. Frequency of diarrhea varies in different reported series from 8-16%[1-2] and is dependent on the dose as well as on the individual susceptibility. Patients with grade 3 diarrhea require hospitalization, intravenous hydration and correction of electrolyte imbalance. Dose reductions are required to prevent the recurrence of severe diarrhea.

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.[6] Fourteen percent of our patients required dose modification. Similar outcomes were reported in a large Italian study.[7] In elderly population of 65-89 years of age the first line capecitabine at a dose of 2000 mg / m² / day gives a response rate of 35% with a low incidence of grade 3/4 toxicity.[8]

All this data supports the use of a reduced dose of capecitabine and taken together with our study which prospectively studies the capecitabine specific side effects in a pretreated subset of patients, it seems that a dose of 2000 mg / m² is a effective with manageable toxicity profile in MBC patients.

It is **concluded** that our study confirms that a lower dose of capecitabine has a good toxicity profile and is active in patients with MBC who have previously received docetaxel.

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