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Eribulin along with capecitabine in relapsed invasive breast cancer- a retrospective single-Institutional study

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ABSTRACT

Background: Invasive breast cancer is the most commonly diagnosed cancer at present. Due to systemic nature of disease, chemotherapy plays an important role in treatment of invasive breast cancer. Relapse (loco-regional or metastatic) is not uncommon in this disease. Both eribulin and capecitabine are effective as single agent in relapsed disease. But in combination, efficacy of these two chemotherapeutic medicines are not properly known. In this single-Institutional retrospective study, Eribulin and capecitabine have been assessed as combination chemotherapy in patients with relapsed breast cancer.

Materials and methods: Patients with relapsed breast cancer, having ER and/or PR positive, Her-2/neu negative or triple negative status and received eribulin alongwith capecitabine, were included in our study. Primary objective of this study was to assess response, progression-free survival (PFS) and overall survival (OS). Secondary objective was toxicity assessment.

Results: 48 patients were included in our study. Median age of patients was 56 years. Thirty six (75%) patients had ER and/or PR positive status and twelve (25%) patients had ER/PR negative status. Five (10.4%) patients achieved complete response (CR). Thirty two (66.7%) patients achieved partial response (PR). Disease was stable (SD) in nine (18.8%) patients. Two (4.2%) patients suffered from progressive disease (PD). Median Progression-free survival (PFS) was 10.15 months. Mean of PFS of patients was 10.72 (95% CI- 9.72-11.72) months. Median overall survival (OS) was 18.15 months. Mean of overall survival of patients was 19.56 (95% CI- 17.9-21.22) months. Nineteen (39.6%) and three (6.2%) patients experienced grade 2 and grade 3 anemia respectively. Eighteen (37.5%) and two (4.2%) patients suffered from grade 2 and grade 3 neutropenia respectively. One patients experienced grade 2 thrombocytopenia. Nineteen (39.6%) patients experienced grade 2 diarrhoea. One patients suffered from grade 3 diarrhoea. Palmo-plantor erythrodysesthesia had been experienced by eight (16.7%) patients. Six (12.5%) patients suffered from grade 2 neuropathy. Two (4.2%) patients experienced grade 3 neuropathy. Fatigue had been experienced by 19 (39.6%) patients.

Conclusion: Eribulin alongwith capectabine can be used in patients with relapsed invasive breast cancer, in whom anthracycline and taxane have previously been used; with response rate and survival better than either single agent chemotherapy. This regimen is important particularly for triple negative breast cancer (TNBC), where option for chemotherapy is limited.

Keywords: Eribulin, capecitabine, relapsed, breast, cancer

INTRODUCTION:

Cancer has become an important barrier to improved life expectancy in the world [1]. Incidence of cancer is rapidly growing in every country. This is mainly due to changes in prevalence and distribution of various risk factors. These changes in many cases are associated with socioeconomic development [2,3]. Invasive breast cancer is the most commonly diagnosed cancer (11.7% of total cancer incidence). Incidence-wise breast cancer has surpassed carcinoma lung (11.4% of total cancer incidence). Other common sites of cancer are- colorectal (10%), prostate (7.3%), and stomach (5.6%) [4]. In our country, breast cancer is now most common cancer in female patients [5]. Increased incidence of invasive breast cancer in recent years is probably due to overall increased exposure to estrogen hormone [6]. Risk factors are also there with change in lifestyle [7].

BRCA1 and BRCA 2 genes are tumor suppressor genes [8]. Mutation of these genes are associated with various cancer, such as malignancy in breast, ovary, fallopian tube, primary peritoneal cancer, carcinoma prostate and pancreas [9,10,11,12]. BRCA1 and BRCA2 germline mutation causes 5% of all invasive breast cancer [13]. 55%-72% of women who inherit BRCA1 mutation and 45%- 69% of women who inherit BRCA2 mutation, will develop carcinoma breast by 70-80 years of age [14,15,16]. High prevalence of mutation in these genes are seen in Ashkenazi Jewish population. Invasive breast cancer associated with BRCA1 mutation, are more likely to be triple-negative [17].

In early stage of disease, treatment of invasive breast cancer is surgery along with chemotherapy, radiotherapy, hormone therapy and targeted therapy depending upon indication of adjuvant treatment. In locally advanced disease, neo-adjuvant chemotherapy followed by surgery is commonly done. After treatment with curative intent in breast cancer, there is chance of loco-regional recurrence (LRR)- which includes in-breast recurrence after breast conservation surgery (BCS), chest wall recurrence after mastectomy and regional recurrence. These account for approximately 15% of all breast cancer recurrence. Predictors of high loco-regional recurrence (LRR) include younger age at diagnosis, higher initial stage of disease, inadequate surgical margins, basal-like and Her-2/neu positive cancer [18].

More than 60% patients with LRR are converted into metastatic disease later on. Shorter disease-free interval, lymph node recurrence, skin lesion predicts greater risk for disseminated cancer. Around 3%-10% patients with breast cancer are diagnosed as de novo metastatic disease [19,20,21]. Up to 30% of patients diagnosed with early stage, develop metastatic disease despite treatment [22]. Most common sites of metastases are bone, lung, liver, brain. Hormone receptor positive tumours more likely metastasize to bone. Hormone receptor negative and/or Her-2/neu positive tumours more likely metastasize in viscera [23]. If burden of metastatic disease is low, then curative intent treatment may be considered. But if disease burden is higher with involvement of multiple distant sites, then systemic therapy with palliative intent is usually considered. In these patients, goal of chemotherapy is to prolong survival, alleviate tumor related symptoms and to improve quality of life [24]. In the previous few years, death rate in invasive breast cancer has decreased largely due to early detection and advancement of therapies [25]. 5-year survival rate in patients with de novo metastatic disease is around 26% [26,27]

In loco-regionally recurrent or metastatic disease, chemotherapy is generally recommended in patients with estrogen receptor (ER) and progesterone receptor (PR) negative breast cancer and patients with ER and/or PR positive disease with symptomatic visceral crisis or with endocrine resistance [27,28]. Most commonly used initial chemotherapy medicines in breast cancer are- anthracyclines, alkylating agent, taxanes, 5-fluorouracil (5-FU).

Common anthracycline medicines are doxorubicin and epirubicin. In studies of previously untreated patients, response rate of doxorubicin is around 50% [29]. But response rate decreases to 30% in patients previously treated with chemotherapy [30,31,32]. Com-

monly used alkylating agent is cyclophosphamide [33]. Most commonly used taxanes in breast cancer are paclitaxel and docetaxel. Response rate to paclitaxel around 48% in patients who have received prior one chemotherapy regimen [34]. In newly diagnosed patients with metastatic disease, response rate is around 62% [35].

5-Flurouracil has been used in the treatment of breast cancer for many years [36]. As single agent, response rate to 5-FU is 25-30% [37]. 5-FU is cell cycle specific medicine. It inhibits DNA and RNA synthesis and function [38].

Above-mentioned chemotherapeutic medicines are used as combination chemotherapy in first-line treatment. Chemotherapy for second and subsequent-line treatment in relapsed breast cancer are gemcitabine, vinorelbine, platinum agents, ixabepilone, capecitabine. Capecitabine is oral prodrug of 5-FU. Capecitabine is converted to 5-FU by the enzyme thymidine phosphorylase. This enzyme is present in higher levels in malignant cells in breast cancer. This explains tumor selectivity of capecitabine to some extent and less systemic toxicity [39]. Capecitabine has been used as combination chemotherapy with taxane [40]. Overall response rate to capecitabine is almost 25% [41].

Eribulin is newer anitneoplastic medicine, belonging to halichondrin class [42]. It binds to high affinity sites on the growing end of microtubule, which probably decreases the effect of eribulin on normal function of microtubule [43,44]. It causes accumulation of tubulin protein, which causes prevention of unstable dynamics of microtubule. This results in mitotic blockade. Mitotic blockade in case of eribulin is irreversible. So, intermittent exposure causes long-term loss of cell viability [45]. This novel mechanism of action probably explains its activity in taxane-resistant relapsed breast cancer.

EMBRACE trial was first phase 3 trial which compared eribulin with treatment of Physician's choice (TPC) in patients with locally recurrent or metastatic breast cancer (MBC) previously treated with at least two chemotherapy regimen, including anthracycline and taxane [46]. In this trial, there was statistically significant improvement in overall survival (OS) compared to TPC. On the basis of this trial, eribulin has been approved as monotherapy for patients with MBC who have received at least two chemotherapy regimen, including anthracycline and taxane.

Both eribulin and capecitabine are effective as single agent in relapsed (loco-regional or metastatic) breast cancer. They have non-overlapping toxicities. There is one phase 1 study combining eribulin and capecitabine [47]. According to this study, eribulin alongwith capecitabine is associated with manageable toxicities and promising clinical activity. This combination was recommended for phase 2 study. On the basis of this study, a retrospective single-institutional study has been done combining eribulin with capecitabine in patients with relapsed (loco-regionally or distant) breast cancer, who have previously received chemotherapy including anthracycline and taxane.

Materials and Methods:

Patients:

In this retrospective single-institutional study, we have analyzed data of patients with relapsed invasive breast cancer, who had been treated with eribulin and capecitabine. Criteria of inclusion in this study was: Patients suffering from relapsed (locoregional or metastatic) breast cancer, treated with eribulin and capecitabine for at least three cycles. Patients, who received eribulin or capecitabine as monotherapy or with other chemotherapeutic medicine, were excluded from our study.

Aims and objectives: Primary objective of this study was to assess response rate, progression-free survival (PFS) and overall survival (OS). Secondary objective was to assess toxicity.

Treatment and follow-up: Patients received eribulin at a dose of 1.4 mg/m2 on Day1 and Day8. Capecitabine had been given at a dose of 825 mg/m2 BD from Day1 to Day14. Cycle had been repeated in every three weeks. Response assessment has been done using Revised RECIST (Response Evaluation Criteria in Solid Tumors)

guideline (version 1.1) [48].Toxicity assessment has been done using EORTC CTCAE, Version 4 (Common Terminology Criteria for Adverse Events) [49].

Eribulin and capecitabine had been continued until disease progression. Clinical examination had been done prior to each cycle of chemotherapy. Radiological investigation had been done after every three cycles of chemotherapy. Any new lesion had been investigated by direct or guided cytological examination. Patients had been followed-up after progression for assessment of overall survival. As long as patients received chemotherapy (Other chemotherapy after eribulin and capecitabine), they were followed-up in every OPD visit. When patients were advised best supportive care, follow-up was done by either OPD visit or by telephonic conversation.

Statistical analysis: Statistical analyses have been done using statistical (SPSS 16) software (Statistical Package for the Social Sciences, Chicago, SPSS Inc) [50]. The means of numerical data have been described as mean ± standard error. Comparison between two subgroups has been done by Independent-samples t-test. Survival analyses also have been done by Kaplan- Meier Survival curve.

Results:

From October, 2016 to November, 2018, total 53 patients (with diagnosis of relapsed invasive breast cancer) received eribulin and capecitabine. Among them, two patients received only one cycles of chemotherapy and three patients received two cycles of chemotherapy (with eribulin and capecitabine). Rest of the 48 patients, who received eribulin and capecitabine for at least three cycles, have been included in our study. Median age of patients was 56 years. Twenty nine (60.4%) patients had locoregional relapsed disease and Nineteen (39.6%) patients had metastatic disease at the time of receiving eribulin and capecitabine. Thirty six (75%) patients had ER and/or PR positive status and twelve patients had ER/PR negative status. All patients were Her-2/neu negative. Five (10.4%) patients achieved complete response (CR). 32 (66.7%) patients achieved partial response (PR). Disease was stable (SD) in nine (18.8%) patients. Two (4.2%) patients suffered from progressive disease (PD). Median Progression-free survival (PFS) was 10.15 months. Mean of PFS of patients was 10.72 (95% CI- 9.72-11.72) months. Median overall survival (OS) was 18.15 months. Mean of overall survival of patients was 19.56 (95% CI- 17.9-21.22) months. . Median follow-up period was 17.75 months.

Three (6.2%) patients experienced grade 3 anemia. Two (4.2%) patients suffered from grade 3 neutropenia. One (2.1%) patients experienced grade 2 thrombocytopenia. One (2.1%) patient suffered from grade 3 diarrhoea. Palmo-plantor erythrodysesthesia was seen in eight (16.7%) patients. Two (4.2%) patients experienced grade 3 neuropathy. Fatigue was seen in 19 (39.6%) patients. (Table 1).

Patients were divided into two subgroups; ER and/or PR positive (subgroup 1) and triple negative (subgroup 2). Thirty six (75%) patients were in subgroup 1 and twelve (25%) patients were in subgroup 2. PFS was 11.38 (95% CI- 10.2-12.56) months in subgroup 1 and 8.73 (95% CI- 7.29-10.17) months in subgroup 2 (Image 1). Difference of PFS between two subgroups was statistically significant (p value- 0.02). OS was

Table 1. Toxicity analysis

	Grade 1	Grade 2
Anemia	26 (54.2%)	19 (39.6%)
Neutropenia	27 (56.2%)	18 (37.5%)
Thrombocytopenia	31 (64.6%)	1 (2.08%)
Diarrhea	25 (52.1%)	19 (39.6%)
Neuropathy	9 (18.8%)	6 (12.5%)

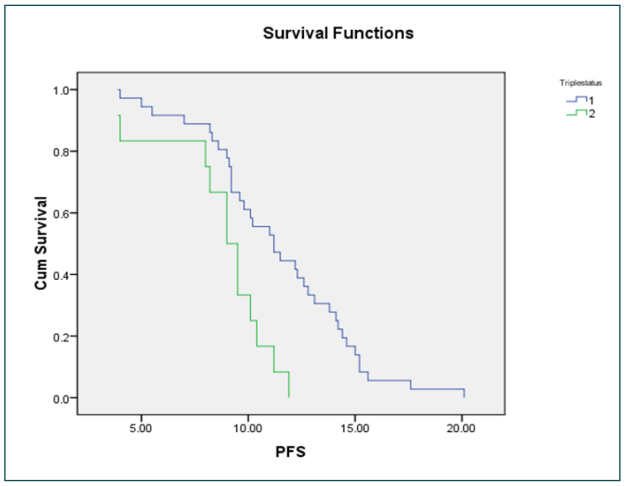

Figure 1. Kaplan-Meier Survival Curve (PFS)

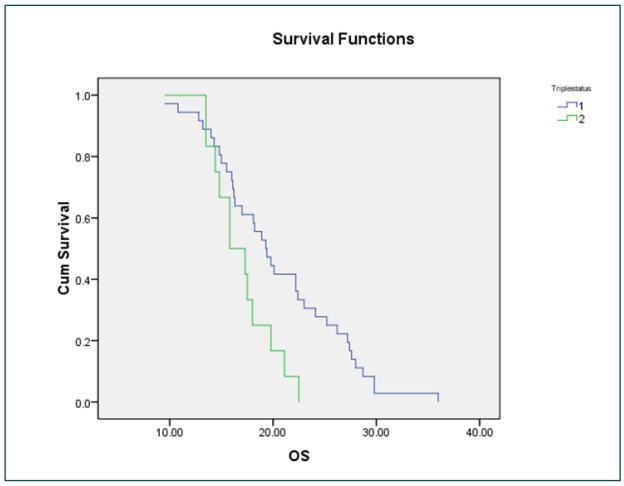

Figure 2. Kaplan-Meier Survival Curve (OS)

20.42 (95% CI- 18.34-22.5) months in ER and/or PR positive subgroup and 17 (95% CI- 15.3-18.7) months in triple negative subgroup (Image 2). Difference of OS between two subgroups was not statistically significant (p value- 0.07). Five patients achieved CR in subgroup 1. Twenty six and six patients achieved PR in subgroup 1 and 2 respectively. In four patients in subgroup 1 and five patients in subgroup 2, disease was stable. Progressive disease was seen in one patient in each subgroup.

Discussion:

Due to systemic nature of invasive breast cancer, chemotherapy plays integral role in its treatment. After advent of systemic therapy in the management of breast cancer, overall survival has improved. Cyclophosphamide, anthracycline, 5-FU and taxane are main chemotherapeutic medicines which are used as first-line therapy in breast cancer. These chemotherapeutic medicines form back-bone of first-line chemotherapeutic regimen.

Capecitabine has been used in breast cancer, particularly as second-line or subsequent chemotherapy. In the study by Lee SH et al, Objective response rate (ORR) of around 26% with capecitabine monotherapy has been seen [51]. Stable disease (SD) has been seen in 34% of patients. Median time to tumor progression (MTTP) was 4.6 months. Median overall survival (MOS) was 18.1 months in this study. Predictors of better OS were hormone receptor positivity, DFS >1 year, fewer number of involved organs, non-refractoriness to anthracycline. In another study by Fumoleau P et al, ORR was 35% [52]. 4% patients experienced CR. Median PFS was 4.9 months. Median OS was 15.2 months. Dose of capecitabine in both the studies was 1250 mg/m2 BD Day1-Day14. In the study by Saeki, T. Et al, dose of capecitabine as monotherapy was 828 mg/m2 BD [53]. In this study, response rate was 45.5%, SD was 31.8%. Median PFS was 6.4 months. In our study, dose of capecitabine was 825 mg/m2 BD; which is similar to study by Saeki et al. Although, response rate is higher than that study. 10.4% patients achieved CR, 66.7% patients achieved PR. Median PFS and OS were also higher than the study by Fumoleau P et al. (Median PFS- 10.15 months, median OS- 18.15 months). Capecitabine montherapy had been used in those studies. But in our study, eribulin alongwith capecitabine had been used. That may be the main reason behind improved response rate and survival in our study.

In EMBRACE trial, eribulin monotherapy has been compared with treatment of Physician's choice [46]. This study has shown statistically significant improved OS with eribulin. Median OS with eribulin was 13.1 months. On the basis of this study, eribulin has been approved as monotherapy in patients with relapsed

breast cancer, who have previously been treated with anthracycline and taxane. One study has been done by Sari M et al, using eribulin monotherapy in heavily pretreated metastatic breast cancer. In this study, ORR was 21.5%. Median PFS and OS was four and forteen months respectively [54]. Response rate in our study is more than the study by Sari M et al. Survival was better than EMBRACE study. Patients in the study by Sari M et al, were heavily pretreated. But in our study, around 80% patients received prior two lines of chemotherapy regimen. Approximately 20% patients received only one chemotherapy regimen (TAC regimen) prior to receiving eribulin/capecitabine. That is probably the reason behind improved response in patients in our study. In our study two chemotherapeutic medicines have been used (Eribulin and capecitabine), combined effect of which probably have an impact of improved survival than EMBRACE study.

Till now, one phase I dose-finding study has been done by Hattori M et al [47]. In this study, eribulin and capecitabine were given in metastatic breast cancer. In this study, dose of eribulin was 1.4 mg/m2. Dose of capecitabine in level 0 was 825 mg/m2 BD and in level 1, it was 1000 mg/m2 BD for 14 days. In this study, level I dosing schedule was recommended due to manageable toxicities. Another phase Ib/II study has been published using combination of capecitabine and eribulin in advanced, treatment-refractory metastatic breast cancer [55]. In this study by Twelves C et al, ORR was 43%. SD was seen in 38% patients. Median progression-free survival (PFS) was 7.2 months. Response rate is more in our study than the above-mentioned phase Ib/II study. It may be due to heavily pretreated patients were included in that study. But in our study, around 80% patients received prior two lines of chemotherapy regimen, approximately 20% patients received only prior one chemotherapy regimen. Probably, for this reason, survival is improved in our study. Predictors of improved response and survival was hormone receptor positivity, previously longer DFS, reduced disease burden at the time of relapse, which were similar to study done by Lee SH et al.

Most common adverse effects of capecitabine were gastro-intestinal effects and hand-foot syndrome (HFS) in the study by Fumoleau P et al. In the study by Lee SH et al, Major toxicities of capecitabine were emesis, diarrhea and HFS. Grade 3 or 4 diarrhea was seen in 3% patients, HFS in 5% patients, Neutropenia in 10% patients. In the study by Sari M et al, most common adverse effects were asthenia (71.4%), neutropenia (46.4%) and peripheral neuropathy (67.9%). In the study by Twelves C et al, toxicities with combination of eribulin and capecitabine included neutropenia, peripheral neuropathy. Neutropenia was mainly asymptomatic. Only two patients experienced febrile neutropenia. Only two patients had grade> 2 neuropathy. No patients in our study suffered from febrile neutropenia. Three (6.2%) patients and two (4.2%) patients suffered from grade 3 anemia and neutropenia respectively. One (2.1%) patient experienced grade 3 diarrhea. Two (4.2%) patient suffered from grade 3 neuropathy. In our study, capecitabine was used at dose of 825 mg/m2 BD. But in the studies by Lee SH et al and Fumoleau P et al , capecitabine was used at dose of 1250 mg/m2 BD. Reduced severity of toxicity in our study was probably due to decreased dose of capecitabine. Incidence of peripheral neuropathy in our study was 35.5%, but in the study by Sari M et al, it was 67.9%. Reason behind this differenece may be heavily pretreatment with chemotherapy in that study. Median number of previous chemotherapy line was four in that study. In our study 20% and 80% patients received prior one and two lines of chemotherapy respectively. Chemotherapy was temporarily stopped for all patients who suffered from grade 3 toxicity. Chemotherapy had been started again with 25% dose reduction, when grade of that particular toxicity reduced to grade 1.

In our study, there is statistically significant difference of PFS between two subgroups. Although, there is no statistically significant difference of OS between two subgroups. Number of patients in subgroup 1 was

36 and in subgroup 2, it was 12. There is significant difference of number of patients between two subgroups. Number of patients between two subgroups should be comparable to find a significant difference between two subgroups.

On comparison to study by Twelves C et al, our study is different in various aspect. In our study, dose of capecitabine was reduced to 825 mg/m2 BD, in contrary to 1000 mg/m2 BD in the study by Twelves C et al. In our study, both PFS and OS have been assessed; but only PFS has been mentioned in above-mentioned study. In our study, subgroup-wise response assessment, survival analyses have been done and significance of difference in survival between two subgroups have been mentioned, which have not been mentioned in the above-mentioned study.

From our study, it is evident that, eribulin alongwith capecitabine is an important chemotherapeutic regimen in patients with relapsed breast cancer. Capecitabine can be used in reduced doses with aim of reduction of toxicity, but with improved efficacy (In combination chemotherapy) with better quality of life. This study was retrospective. This is one of the limitation of our study. This study was single-Institutional. This may be the cause of relatively small number of patients in this study. This is single-arm study. So, comparison with single chemotherapeutic medicine or standard chemotherapeutic regimen could not be done. In future, this limitations can be overcome by prospective, randomized, comparative multi-Institutional study.

Conclusion:

Eribulin alongwith capectabine can be used in patients with relapsed (locoregional or distant) breast cancer, particularly in Her-2/neu negative status, in whom anthracycline and taxane have previously been used; with response rate and survival better than either single agent chemotherapy. This regimen is also important in patients with TNBC, where option for chemotherapy is limited.

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