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Neoadjuvant Platinum Based Chemotherapy in Triple Negative Breast Cancer-Preliminary Experience from A Tertiary Cancer Centre.

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Abstract: Triple negative breast cancers are found to have poor prognosis. It has been postulated that pathological complete response (pCR) to neoadjuvant chemotherapy can be a surrogate for survival in TNBC. Various combinations of chemotherapeutic agents have been tried to improve the pCR rates including addition of platinum compounds. Although western data is available no studies till date have reported this from a developing world. This study intends to find out the pCR rates and the disease free survival and the overall survival for patients treated with neoadjuvant chemotherapy (NACT) with paclitaxel and carboplatin in locally advanced TNBC. The study was conducted at a rural tertiary cancer centre in South India. This was a retrospective analysis of medical records of patients who underwent NACT with paclitaxel and carboplatin from 1st January 2014 to 31st December 2018 at. Malabar Cancer Centre. A total of 33 patients underwent chemotherapy with paclitaxel and carboplatin during the study period. The median age was 51 years. 59% of patients had stage IIIA disease.96% of patients took all 12 cycles of NACT. 43% of patients had complete response to neo adjuvant chemotherapy whereas 57% of patients had partial response to chemotherapy. This was comparable to the available literature. The four year disease free survival was 81% and the four year overall survival was 86% in this study. No statistically significant difference in survival could be found in those patients who achieved pCR when compared to those who did not. Studies with a larger number of patients are needed to throw light in this aspect.

Keywords: Triple negative breast cancer, Paclitaxel and carboplatin, pathological response, Disease free survival, Overall survival

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1. INTRODUCTION

Triple negative breast cancer (TNBC) is a group of breast cancers which are designated so because of lack of expression of the estrogen(ER), progesterone (PR) or her 2 receptors. Triple negative breast cancer accounts for about 20%of breast cancer cases diagnosed globally[1]. It occurs more commonly in women younger than 40 years of age and carries worst prognosis among all the breast cancer subtypes [2]. At Least six different molecular subtypes of triple negative breast cancer are described which includes two basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) [3]. Lack of targeted therapies and limited knowledge about the disease biology are often a challenge to the treating physician[4]. The standard treatment protocol in locally advanced triple negative breast cancer consists of neoadjuvant chemotherapy (NACT) to downstage the tumor followed by surgery, adjuvant chemotherapy and radiotherapy. Standard neoadjuvant chemotherapy regimens include a combination of anthracyclines, taxanes, and cyclophosphamide[5,6]. Platinum-based chemotherapy has been proposed but is not yet recommended by available guidelines. Also there are no approved targeted therapies for TNBC in the neoadjuvant setting, Because of the lack of approved targeted agents, cytotoxic chemotherapy still remains the mainstay of systemic treatment. Conventional neoadjuvant chemotherapy regimes in TNBC results in pathological complete response rates varying from 27 - 45%[7]. It is also postulated that pathologic complete response is a surrogate for good event free survival in breast cancer [8]. Data from the analysis of five clinical trials [8-11], conducted in TNBC patients treated with neoadjuvant platinum-containing therapies combined with taxanes, showed a pCR rate ranging from 33% to 67%. The use of platinum agents has been tried in the treatment of TNBC. There are molecular and histopathological similarities between BRCA1-mutated breast cancer and TNBC and TNBC is strongly associated with germline mutations in the BRCA1 gene and it is postulated that 90% of BRCA1-mutated tumours are TNBC[12]. Also DNA repair mechanisms are deficient in cells with BRCA1 mutations and this makes them more sensitive to platinum agents[13]. Two studies investigated the addition of carboplatin to standard-combination neoadjuvant chemotherapy regime in patients with TNBC. The CALGB 40603 study [14]was a phase 2 trial that investigated the benefit of adding carboplatin, bevacizumab, or the combination to taxane/ anthracycline-based chemotherapy. They found that the addition of carboplatin significantly increased the pCR rate compared with control, from 46% to 60%.However, in the subsequent survival analysis, it was found that adding carboplatin did not significantly impact survival outcome[15]. These results are in conflict with those in the Gepar-Sixto trial[15]. In GeparSixto a total of 595 patients were enrolled into two groups, with both groups receiving weekly paclitaxel, weekly liposomal doxorubicin, and bevacizumab every 3 weeks. The experimental arm additionally received carboplatin weekly. They showed that the addition of carboplatin resulted in a significantly improved pCR rate from 37% to 53% over control .This translated into an absolute benefit in 3-year event free survival of 9.7% for the addition of carboplatin over control. Keeping these two studies in mind, the decision to add carboplatin to a NACT regimen remains a highly individualized one. Studies looking at the impact platinum compounds on pathological complete response and survival outcomes are scarce from the developing world. So far no published Indian data is available regarding data on the impact of NACT with paclitaxel and carboplatin on survival. Hence we aim to study the pCR of paclitaxel and carboplatin NACT regimen and survival outcomes in this setting. To find out the treatment outcomes in terms of pathological complete response, disease free survival and overall survival in locally advanced triple negative Breast cancer patients treated with neo adjuvant paclitaxel and carboplatin chemotherapy regimen who underwent treatment from 1st January 2013 to 31st December 2018 at a tertiary cancer centre in South India.

2. METHODS

This was a retrospective cross sectional record based study. The study was conducted at a tertiary cancer centre in South India. Malabar Cancer Centre, Thalassery is a major cancer care provider in Northern district of Kerala. It is a tertiary care cancer center under the Government of Kerala. All patients of locally advanced TNBC who underwent Neodjuvant chemotherapy (NACT) with paclitaxel and carboplatin from 01st January 2014 to 31stDecember 2018 were included in the study. Those patients who underwent NACT with other regimes and case records with more than 50% of missing data were excluded from the study. Triple negativity was confirmed by the tests which were carried out with standard Food and Drug Administration approved kits by Immunohistochemistry. Antibody staining of a set of paraffin embedded slides for ER and PR was carried out for each patient. A HER-2 report of 3 + by IHC was considered to be Her 2 positive. Those with scores who were 2+, confirmation was done by Fluorescent insitu hybridization (FISH). HER-2 score of 0 or 1 was considered negative. Cases were discussed in a multispeciality tumor board comprising Surgical oncologist, Medical Oncologists, Radiation oncologists, Radiologists and Neuropathologists. The decision for sending a patient to NACT was as per tumor board consensus. Paclitaxel was given at a dose of 80mg/m2 and carboplatin at AUC 2 as per protocol. Chemotherapy was administered only if absolute neutrophil count was more than 1500/cu.mm and platelet count was more than 100 000/cu.mm. Chemotherapy was given on an outpatient basis at our day care chemotherapy unit. After the completion of the planned course of chemotherapy clinical response was documented and patients were then taken up for surgery. After surgery patients were given systemic chemotherapy with Adriamycin (60mg/m2) and Cyclophosphamide (600mg/m2) for 4 courses repeated every 21 days. Following completion of chemotherapy patients were then treated with adjuvant radiation therapy. Adjuvant radiation dose was 40Gy in 15 fractions in the post mastectomy setting and 40 Gy in 15 fractions followed by 10 Gy in 5 fractions boost if the patient underwent breast conservation surgery. After that patients were kept at regular follow up 4 monthly for the first 2 years,6 monthly at three to five years and yearly thereafter as per institutional protocol. The data pertaining to patients were derived from record review of case records available in the Medical Records Department of Malabar Cancer Centre. Data regarding details of chemotherapy was collected from the chemotherapy charts maintained. Thus, routinely reported data was abstracted into the structured study instrument. The Principal Investigator and Co-Investigators were responsible for data collection. The data variables included demographic details like age and stage of the disease, number of chemotherapy cycles taken and pathological response post

chemotherapy and were recorded from medical records. Pathological response post NACT was graded as per American Joint Committee on Cancer (AJCC) criteria[17]. Complete response (CR) was defined as the absence of invasive carcinoma in the breast and lymph nodes. Partial response (PR) was defined as a decrease in either or both Tumor or Nodal stage compared to the pretreatment T or N, and no increase in either T or N. No response (NR) was defined as no apparent change in either the T or N categories compared to the clinical pretreatment assignments, or increase in either the T or N categories at the time of pathologic evaluation. Disease Free Survival was calculated from the date of surgery to date of recurrence / metastasis/last follow up. Overall Survival was calculated from the date of diagnosis to date of death/date of last follow up.

3. STATISTICAL ANALYSIS

The data was entered in Microsoft excel and analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 20.0. Continuous variables such as age was summarized in terms of either mean ± standard deviation or median (Inter quartile range) depending on the statistical distribution of data. Categorical variables were expressed in terms of frequency and percentage. Survival analysis was done using Kaplan Meier.

3.1 Ethics Considerations

Data for this study was collected routinely from the hospital records. Approval of the Institutional Review Board was obtained for conducting this study. While names of patients were referred to compare data across registers, the data abstraction form did not contain the name or any other personal identifiers. Since this was a retrospective study the ethical clearance was waived off.

4. RESULTS

A total of 33 patients were analyzed. The median age was 51 years (ranged from 26 to 72 years).Baseline characters are summarized in Table 1.

Table 1: Baseline characteristics of the study population

Age	**Less than 50 years (number of patients) 14(42%)**	**50 or more 19(58%)**		
Menstrual status	Premenopausal 15(46%)	Postmenopausal 18(54%)		
Stage	II B 7(21%)	IIIA 20(61%)	IIIB 5(15%)	IIIc 1(3%)
Number of chemotherapy cycles	12 cycles 32(97%)	10 cycles 1(3%)		

59% of patients had stage IIIA disease.96% of patients took all 12 cycles of NACT and one among them developed allergic reaction to carboplatin after 6 cycles and further chemotherapy was given with paclitaxel alone.1 patient developed grade 3 neuropathy and only 10 cycles could be given.

4.1 Response to Neoadjuvant Chemotherapy

Out of the 33 patients 2 patients had clinical progression post Neo adjuvant chemotherapy. One patient developed lung metastasis and one had locally inoperable disease and was not willing for any further treatment and both were not taken up for surgery. They were then taken up for palliative intent treatment. So pathological response could be assessed in 31 patients. 43% of patients had complete response to neo adjuvant chemotherapy whereas 57% of patients had partial response to chemotherapy. Out of 31 patients who underwent surgery 29 patients underwent mastectomy and 2 patients underwent breast conservation surgery.

4.2 Disease free Survival

On follow up 3 patients developed systemic metastasis mainly to lungs and liver. The four year disease free survival was 81% in this study. The disease free survival is shown in Figure 1.

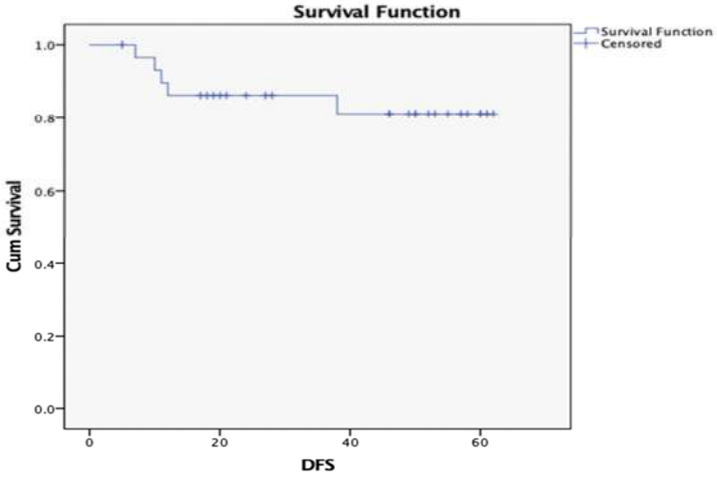

Fig 1: Disease free survival

4.3 Overall Survival

3 patients died due to disease progression and one patient died due to cardiac issues while on follow up. The four year overall survival was 86% in this study. The overall survival is shown in Figure 2.

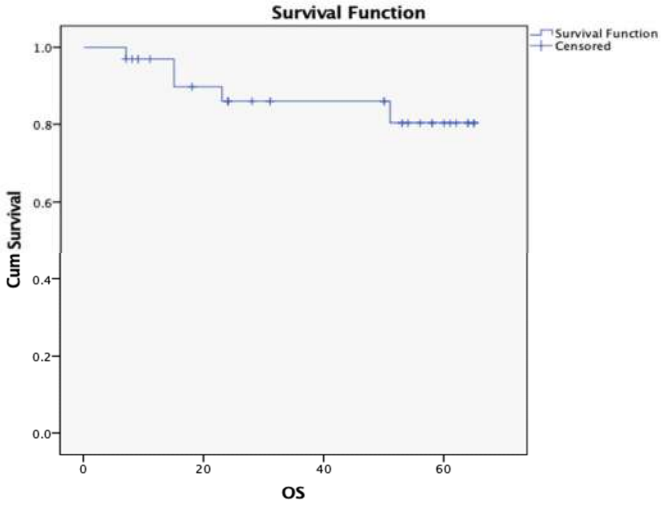

Fig 2: Overall survival

4.4 Pathological Complete Response and Disease Free Survival

4 yr DFS in patients who had pathological complete response (pCR) was 82.5% while it was 82.4% for those who did not and the difference was not statistically significant (p-0.838).This is shown in figure 3.

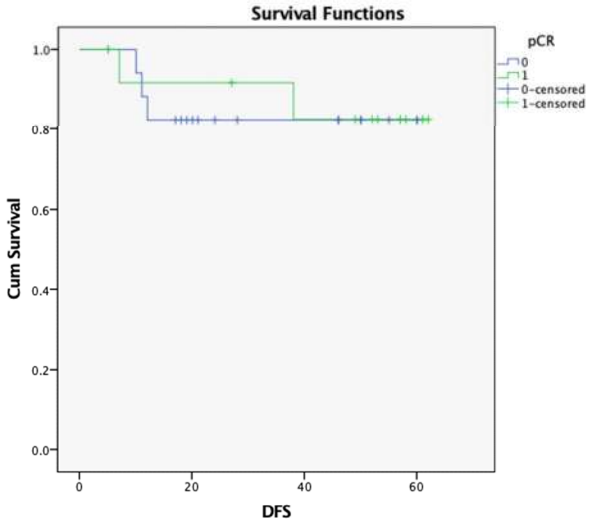

Fig 3: Pathological complete response and disease free survival

4.5 Pathological complete response and overall survival

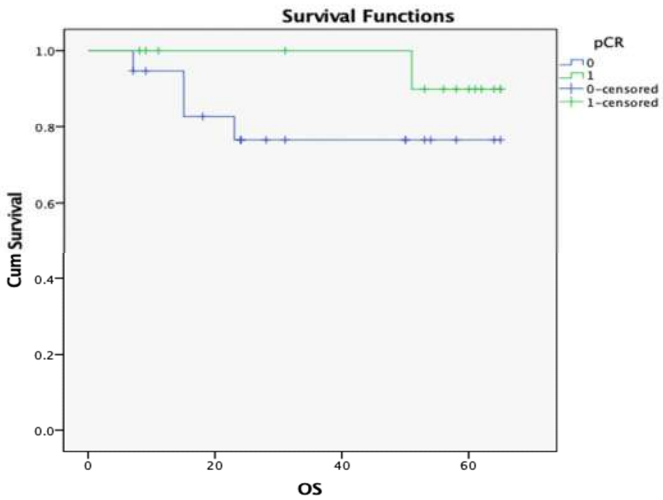

Fig 4: Pathological complete response and overall survival.

4 yr OS in patient who had pCR was 90% while it was 76.5% for who did not .Although the survival curves showed wide separation this difference was not statistically significant (p-0.20).This may be due to the low sample size in our study. This is given in Figure 4,

5. DISCUSSION

To our knowledge this is the first Indian data regarding survival outcome in triple negative breast cancers treated with neoadjuvant paclitaxel and carboplatin. As of now no targeted therapies are currently approved for TNBC in the neoadjuvant setting. We need to rely mainly on chemotherapies with the goal of increasing pCR rates. Addition of carboplatin to the standard taxane, anthracycline regime was evaluated in an attempt to increase the pCR rates. 33 patients underwent NACT with Paclitaxel and Carboplatin during the study period. This drug combination was well tolerated by most patients. In our study, 96% patients completed all the 12 cycles of chemotherapy and among them all except one completed 4 courses of adjuvant Adriamycin and Cyclophosphamide chemotherapy. In a study by Castrellon et al 91% of the patients received all 12 cycles of NACT with paclitaxel and carboplatin and 88% received all four planned cycles of anthracycline chemotherapy[18]. As per the CALGB 40603 study[14], the addition of carboplatin increased the pCR rate from 46% to 60% and this difference was statistically significant (P = .0018). In the phase II GeparSixto trial[16], the addition of carboplatin increased pCR from 37% in the control group to 53% in patients that received carboplatin (P=0.005).The pathological complete response rate in our study was 43%. The grade 3 toxicities that we had was grade 3 neutropenia in one patient and grade 3 neuropathy in another patient. Also one patient developed an allergic reaction to carboplatin after 6 cycles and further carboplatin could not be given. No grade 3 or 4 thrombocytopenia occurred. The incidence of grade 3 or 4 neutropenia was 37.8% and the incidence of grade 3 or 4 thrombocytopenia was 6% as shown in a combined analysis of 6 randomized control trials [19-23]. Also the incidence of grade 3 or 4 neuropathy was 3.6% in those trials. Median follow-up was 39 months in the CALGB study[15] and 47.3 months in the GeparSixto GBG66 study[16]. The median follow up in our study was 48 months. Both these studies showed no significant differences in DFS nor in OS with the addition of carboplatin. In our study also no difference in overall or disease free survival based on pathological complete response were obtained. Although the overall survival curves showed separation this difference was not statistically significant. The limitations of our study include the less number of patient populations. In a meta analysis conducted by Sandhu et al [24] the prevalence of TNBC in India ranged from 27 to 35% with an average of 31%.In a study conducted at a tertiary cancer center in Kerala, South India the prevalence of TNBC was found to be 17%[25]. The low prevalence of TNBC in our region and the fact that only locally advanced TNBC will undergo neoadjuvant chemotherapy might be the reason for the less number of patients in our study.

6. CONCLUSION

A combination of paclitaxel and carboplatin chemotherapy is a feasible and tolerated option in triple negative breast cancer patients. But data from large randomized studies are needed to find out the impact of pathological complete response and overall survival. Since TNBC represents a heterogeneous group of diseases it is important to point out that further studies will be needed to individualize treatment according to the different subgroups of TNBC. Once we are able to identify the patients who are likely to benefit, this can in turn lead to improved pathological response rates and improved treatment outcome. With the available data, the addition of carboplatin to the standard chemotherapy should be individualized.

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8. AUTHORS CONTRIBUTION STATEMENT

Dr Praveen and Dr Joneetha conceptualized and gathered the data with regard to the work. Dr Praveen analyzed the data and Dr Chandran K Nair and Dr Priya Rathi gave their valuable inputs in designing the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

9. CONFLICTS OF INTEREST

Conflict of interest declared none.

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