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Dose dense chemotherapy in breast cancer patients – a single center experience from south India

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Abstract

Purpose*- To study the tolerability and adherence to the dose dense chemotherapy in high risk breast cancer patients from India.*

Patients and Methods*- It was a retrospective data with single center experience of dose dense chemotherapy in high risk breast cancers (BC) like , triple negative breast cancers (TNBC) and human epidermal growth factor receptor 2 (HER2) positive BC with size equal or above 0.5cm , Hormone positive BC of size above 5cm, >= 1 regional lymph node positive tumors. Four cycles of doxorubicin and cyclophosphamide (AC) followed by 4 cycles of sequential paclitaxel (T) were given in 2 weekly schedules. The toxicity profile and adherence to the treatment were analyzed.*

Results.

Total 101 patients were analyzed from January 2020 to July 2021. All the patients completed the planned chemotherapy. Grade 3 and 4 febrile neutropenia (FN) accounted to 3%, grade 3/4 anemia was seen in 8% of patients. No grade 3 and 4 Chemo induced nausea and vomiting (CINV) was seen. Grade 3 and 4 mucositis was seen in 2% and diarrhea in 1% of the patients. Grade 3 and 4 sensory neuropathy was seen in 2% of patients. Cardiac dysfunction was seen with sequential trastuzumab in 4%. Dose reductions were seen in 2% of patients and treatment delays by a week was seen in 2% of patients due to FN.

Conclusion*- Dose dense chemotherapy was well tolerated in Indian patients with decreased CINV, myalgia and arthralgia due to improved supportive care.*

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I. Background

Breast cancer was the most common cancer prevalent in India among females. Globocan 2020 data showed that incidence of breast cancer was 1, 78,361 cases with mortality of 90,408 cases in year 2020 (1). A significant number of breast cancer patients in India were younger (less than 40 years) with associated aggressive histologies (2). Even though breast cancer is a highly curable disease in early stages (3), but unfortunately majority of the breast cancer patients in India present with locally advanced disease and in inoperable condition (4,5). To improve the survival outcomes EBCTCG meta-analysis showed anthracycline based chemotherapy has better outcomes than cyclophosphamide, methotrexate, 5 flouro uracil based regimen(CMF) (6). NSABP B 36 study suggested AC chemotherapy had less toxicities with equivalent survival outcomes when compared to 5 Fluoro uracil, epirubicin, cyclophosphamide regimen (FEC) (7). CALGB 9344 had showed addition of taxane sequentially to AC chemotherapy had improved survival outcomes without increasing mortality (8). Anthracycline taxane based chemotherapy at 3 weekly schedules in adjuvant setting increased disease free survival, overall survival in high risk patients. Norton hypothesis and gompertzian hypothesis suggested decreasing the duration between chemotherapy cycles enhances tumor cell kill and improves survival (9). CALGB 9741 trial showed that patients who received adjuvant chemotherapy with doxorubicin cyclophosphamide followed by taxanes at 2 weekly intervals (dose dense chemotherapy) had better survival outcomes when compared to 3 weekly schedules (10). Various other studies like NSABP B38 also showed dose dense chemotherapy had better survival outcomes and became the standard of care (11). Even though guidelines (12) suggest for dose dense chemotherapy in high risk breast cancer patients but unfortunately majority of the centers in India still practice 3 weekly schedule. The reasons to avoid dose dense chemotherapy are fear of toxicities and delayed recovery of cytopenias in Indian patients. The majority of studies related to dose dense chemo were studied in western population who completed the chemotherapy with acceptable

toxicities. But in India, majority of patients are malnourished with decreased Body mass index in comparison to western population (13, 14). Literature related to dose dense chemotherapy in Indian patients is sparse. Hence, we studied this regimen in Indian patients in relation to their toxicity profile and acceptability to chemotherapy.

II. Methods

Patient's selection and study design

It was a retrospective descriptive data collected at a tertiary care hospital HCG Cancer center, Visakhapatnam. The data was collected from the records of the patients treated between January 2020 to July 2021. It included all the patients who were treated with dose dense chemotherapy in stage 1 to stage III breast cancers. Both male and female patients between 18 years to 70 years with Karnofsky Performance Status index>= 80 were included. The patients with both unilateral and bilateral breast cancers were included.

All the patients had undergone receptor status examination for estrogen and progesterone receptor, HER 2 receptors by standard immune histo chemistry (IHC) techniques on either core biopsy or surgical specimens. Tumors with equivocal HER 2 receptor status had undergone fluorescent insitu hybridization (FISH) testing. The patients were screened for metastasis by relevant imaging methods. All patients were screened for adequate cardiac function.

Patients received chemotherapy either in neo adjuvant setting or in adjuvant setting. The indications to start adjuvant dose dense chemotherapy in these patients were, in hormone positive BC patients tumor size more than 5 cm, in TNBC and HER2 positive BC patients T size more than 0.5 cm with or without nodal positivity, BC with any regional node positivity (>= 1 lymph node).The indications for neoadjuvant chemotherapy (NACT) were T4stage, N2 and above nodal status, T2 in TNBC and HER2 positive BC

Treatment schedule

Patients in the study received total 8 cycles of chemotherapy. Initially 4 cycles of doxorubicin 60mg per m2 with cyclophosphamide 600mg per m2 (AC) were given intravenously (IV) at 2 weekly schedule. Subsequent 4 cycles of paclitaxel 175mg per m2 (T) was given IV every 2 weekly. Anti-emetic medication with aprepitant 125mg on day 1, 80mg on day 2 and 3, and olanzapine 10mg from day 1 to 4 were given orally along with AC regimen. Pegfilgrastim 6mg (PEG GCSF) subcutaneously was given on day 2 of AC chemotherapy. Analgesics like tramadol and ibuprofen were given for a period of 10 to 14 days after each paclitaxel infusion. All the patients were screened for adequate hemogram (Hemoglobin (Hb) above 8gm/dl, White Blood Cell (WBC) count more than 4000/cumm or Absolute neutrophil count (ANC) > 1500 /cumm, platelet count of >1 lac/cumm), normal liver and renal function tests before each course of chemotherapy. HER 2 positive breast cancer patients received adjuvant trastuzuamb loading dose 8mg per kg and maintenance dose 6mg per kg for one year after completion of dose dense chemotherapy. Patients who received neoadjuvant chemotherapy had completed all the 8 cycles before surgery. Patients had undergone modified radical mastectomy (MRM) or breast conservation surgery (BCS) either upfront or post NACT. Patients who received NACT were assessed for pathological complete response (PCR) in their surgical specimens.

Study assessments

The primary objective of this study is to see the tolerance of dose dense chemotherapy in breast cancer patients in India. The post chemotherapy side effect profile was evaluated for all the patients based on CTACAE v 5.0 criteria. The adherence to treatment and acceptance to further continue dose dense chemotherapy was also studied.

III. Results.

Base line characteristics

Between 1 January 2020 to 31 July 2021, a total of 101 patient's records were analyzed for the study. The female patients were 100 and male patient was 1. The median age in the study was 48 years (range 28 to 70 years). The patients younger than 40 years were 24 (24%) and age from 40 to 70 years were 77 (76%). There were 48 (48%) rural patients and 53(52%) patients were from urban areas. Comorbid illness like diabetes, hypertension, hypothyroidism, seizure disorder, HIV infection, chronic kidney disease were documented in 28 (28%) patients in the entire cohort. There were around 43 (43) premenopausal and 58 (57%) post-menopausal patients in the study. The nulliparous patients were 8 (8%) and remaining were multiparous (92%). Family history of breast cancer, colon ca, prostate ca, ovary ca, cervical ca, head and neck ca were documented in 14 patients (14%). The body mass index (BMI) of these patients showed, normal BMI(18.5 to 24.9 kg/m2) in 60 (59%), overweight (25 to 29.9 kg/m2) in 25 (25%), obese (equal or above 30kg/m2) in 10 (10%), undernourished(< 18.5kg/m2) in 6 (6%) patients.

Tumor related factors like histopathology was invasive ductal type in 98 (97%), lobular type in 2 (2%) and metaplastic type in 1 (1%) patients. Grade 1 tumors consisted of 5 (5%), grade2 in 50 (49%), and grade 3

were seen in 45 (45%) patients. Estrogen and or progesterone receptor (HR) positive and HER 2 negative BC were seen in 26 (26%) patients, TNBC in 33 (32%) patients, HER2 positive with HR positive patients were 22 (22%) and HER2 positive with HR negative were seen in 20 (20%) patients.

Treatment factors like BCS were done in 7 (7%) patients and MRM was done in 94 (93%) patients. NACT was received in 25 (25%) patients and adjuvant chemotherapy was given to 76 (75%) patients. PCR was achieved in 8 (8%) patients who received NACT. Trastuzumab was given in 42 (42%) patients for 1 year after the completion of chemotherapy.

Tolerance to chemotherapy

All the patients in the study group completed the planned 8 cycles of chemotherapy. Mortality or disease progression was not seen in the study group during the chemotherapy and trastuzumab therapy. Grade 3 FN was seen in 3 (3%) patients after anthracycline based chemotherapy. They were stratified to low risk FN and were treated with oral antibiotics and with additional courses of GCSF on outpatient basis. One patient developed FN in 2nd cycle with delayed ANC recovery by more than a week. Her subsequent doses of AC chemo was decreased to 75 % dose. The remaining 2 patients were changed to 3 weekly schedule with same dose. Grade 3 anemia was developed in 8 (8%) patients. They were managed with packed red cell (PRBC) transfusion. Grade 3 or 4 CINV was not seen in any of the patients. Grade 3 mucositis developed in 2 (2%) patients. Alopecia was seen in all patients. Grade 3 peripheral sensory neuropathy after paclitaxel infusion was seen in 2 (2%) patients. Both of them were managed with IV and oral analgesics. Nab paclitaxel was substituted for 1 patient in subsequent cycles and the other patient was given 75 percent dose of paclitaxel. Cardiac dysfunction with decreased left ventricular ejection fraction (LVEF < 50%) was seen in 4 (4%) patients during trastuzumab therapy. All the patients recovered in cardiac function to LVEF >55% and received further cycles of trastuzumab. Treatment delay by more than a week was seen in 2 (2%) patients due to FN. Treatment delay of 1 to 6 days was seen in 32 (32%) patients.

IV. Discussion

Our study results showed that in Indian patients the tolerability to dose dense chemotherapy is meaningful. Majority of the patients tolerated the toxicities due to chemotherapy and were compliant to treatment. Four major trials like CALGB 9741, NSABP B38, GIM2 trial (15) and GONO MIG trials (16) extensively studied dose dense chemotherapy in western population. NSABP B38 clinical trial showed the improved survival outcomes with dose dense chemotherapy which was unquestionable and hence became the standard of care. Majority of the patients in those trials completed therapy with minimal grade 3 /4 toxicities. In our study Grade 3/4 FN was seen in 3% of the patients which was comparable to the above mentioned clinical trials. All the patients were managed with oral antibiotics. None of them required hospitalization or IV supportive therapy where in CALGB 9741 trial 2% of the patients hospitalized due to FN. Grade 3/4 anemia was seen in 8% of our patients where as in above clinical trials it was less than 3%. This might be due to poor oral intake and endemic nutritional deficiency in Indian population. In majority of our patients, the baseline Hb was below the lower limit of normal prior to chemotherapy (17, 18). Chemotherapy was given only if Hb is more than 8 g/dl. PRBC transfusion was done in patients with Hb less than 8gm/dl. Grade 3 CINV was not seen in any of our study population but it was 14% in CALGB 9741 trail, 12% in GONO MIG trial, 4% in GIM 2 trial, and 6% in NASBP B38 study. This was due to use of dual antiemetics like aprepitant and olanzapine (19) as suggested by recent evidence where as in above trials olanzapine was not used as antiemetic medication. Grade 3 mucositis and diarrhea was seen in 2% and 1% of the patients respectively in our study which is comparable with other trials. Grade 3/4 peripheral sensory neuropathy was seen in 2% of our patients where as it was 4% in CALGB 9741 and GIM2 trial and 7% in NSABP B38 trial. Grade 3/4 myalgia and arthralgias was not seen in our patients and in other studies it accounted to 5 to 11%. This could be due to usage of prophylactic analgesics (20) for 10 to 14 days depending on symptoms. Cardiac dysfunction was not seen in our patients during anthracycline therapy similar to other trials but 4% of the patients had decreased in LVEF with sequential trastuzumab. All of the patients recovered subsequently and completed 1 year of trastuzumab. The dose reduction in chemotherapy was done only in 2% of the patients where it was 13% in CALGB 9741 trial, and 2% GONO MIG trial. Treatment delays by a week accounts to 2% of our study patients due to FN and delays of 1 to 6 days accounts to 32%. It was purely due to hospital administrative and patient's personal reasons rather than medical grounds. In CALGB 9741, GONO MIG trials the treatment delays accounts to 6% and 19% respectively. Overall our study showed that our patients well tolerated the treatment and toxicities were comparable to western data. In fact, the newer advances in supportive care in cancer like dual antiemetics study by Rudolph et al and ibuprufen therapy for taxanes by Julie et al improved the quality of life during treatment. The additional advantage of the 2 weekly chemotherapy is, short duration and earlier cessation of entire treatment.

The limitations of our study were it was a retrospective descriptive study unlike the above discussed clinical trials which were phase III Randomized Controlled Trials. It was a single center experience with limited number of study population. So it lacks the heterogeneity in treatment tolerance among different patient groups. The addition of PEG GCSF to chemo increased the cost of therapy to the patient. The addition of olanzapine to antiemetic regimen increased the sedation and drowsiness in majority of the patients. Hence it was prescribed to take during sleeping hours. The study period was 18 months with short follow-up and didn't estimate the survival outcomes. We require large number of patients and longer followup, to study the survival outcomes.

V. Conclusion.

Our study suggests that Indian patients well tolerated the dose dense chemotherapy with limited toxicities. It warrants further research in larger cohorts to study better outcomes.

Table 1

Demographic factors	**Number of patients (%)**	**Tumor related factors**	**Number of patients (%)**
Total patients	101	Ductal ca	97%
Females	100	Lobular ca	2%
Males	1	Metaplastic ca	1%
Median age	48years	Grade I	5%
Age <40years	24%	Grade II	49%
Age 40-70years	76%	Grade III	45%
Rural patients	48%	ER+/-PR positive	26%
Urban patients	52%	TNBC	32%
Comorbid illness	28%	HER 2+, ER/PR –	20%
Premenopausal	43%	HER2+ER/PR +	22%
Post-menopausal	57%	**Treatment factors**	
Nulliparous	8%	B C S	7%
Multiparous	92%	MRM	93%
Family history of cancer	14%	Neoadjuvant chemotherapy	25%
BMI 18.5 – 24.9kg/m2	59%	Adjuvant chemotherapy	75%
BMI 25-29.9kg/m2	25%	Pathological complete response	8%
BMI >30kg/m2	10%	Trastuzumab received	42%

Table 2

Parameter/clinical trial	Our study	CALGB9741	NSABP B38	GIM2	GONO MIG
Grade 3or4 FN	3%	3%	3%	<1%	<1%
Anemia <8g/dl	8%	1%	2%	1%	3%
Thrombocytopenia grade3 or 4	-	4%	-	<1%	1%
Fatigue grade3or 4	5%	-	8%	3%	1%
Nausea grade3 or4	0%	8%	3%	3%	
VomitingsGrade3 or4	0%	6%	3%	1%	12%
Mucositis grade3or4	2%	3%	<1%	1%	3%
Diarrhea grade3 or 4	1%	1%	2%	1%	1%
Sensory neuropathy grade3 or 4	2%	4%	7%	4%	0%
L V dysfunction	4%(on trastuzumab)	1%	0%	0%	0%
Arthralgia grade 3or4	0%	5%	11%	2%	6%
Dose reductions in chemotherapy	3%	13%	-	-	2%
Delay of chemo by a week	2%	6%	-	-	19%
Hospitalization due to FN	0%	2%	-	-	-

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