A Comparative Study of Cisplatin Plus Adriamycin Compared with Cyclophosphamide Plus Adriamycin in Patients with Untreated Metastatic TNBC

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Abstract

Objective: To look for the response of platinum agents in BRCA unknown TNBC patients as it is a cheaper drug and readily available.

Material and Methods: This study was comparative, conducted in department of Medical Oncology and Radiotherapy from May 2019 to Februaray 2021 in which a total of 290 (145 in each arm) patients of metastatic TNBC were enrolled. A total of 290 patients (145 in each arm) of symptomatic metastatic TNBC were randomized into 2 groups. Group A received Adriamycin (60mg/m²) plus Cisplatin (75mg/m²) while Group B received Adriamycin (60mg/m²) plus Cyclophosphamide (600mg/m²) on day 1 of 21 days cycle for a total of 4 cycles. The response was assessed using RECIST criteria v.1.01. National Cancer Institute Common Toxicity Criteria version 4.03 (CTCAE) was used to document toxicities. Health-related quality of life was determined using EORTC QLQ- C30 with a minimum decrease of ≥ 10 points considered significant.

Data was analyzed using spss version 23. The quantitative variables were presented as mean ±SD while qualitative variables like tumor response as percentage and frequency. An Independent sample t-test with a confidence interval of 95% was used for comparison between groups and a p-value of < 0.05 was taken as significant.

Results: In group A, 33(22.8%) and 67(46.2%) showed complete and partial responses respectively while stable and progressive disease was noted in 25(17.2%) and 20(13.8%). In group B, 23(15.9%) had complete response while 66(45.5%), 41(28.3%), and 15(10.3%), showed partial response, stable and progressive disease respectively (p=0.094) ORR between groups was 69.0% vs.61.4%. More grade ¾ neuropathy (p=0.004) and nephropathy (p=0.00007) was seen in group A. Quality of life was comparable in both groups(p=0.540)

Conclusions: No statistically significant difference in noted between two treatment arms but patients in the Cisplatin arm experienced more neuropathy and nephropathy.

Keywords: TNBC, Cisplatin, metastatic

How to cite: *Yaqub S, Khokhar MA, Zafar A, Goraya AW, Rauf A, Niazi ZAK. A Comparative Study of Cisplatin Plus Adriamycin Compared with Cyclophos-phamide Plus Adriamycin in Patients with Untreated Metastatic TNBC. Esculapio - JSIMS 2023;19(03):355-358*

DOI: https://doi.org/10.51273/esc23.251319320

Introduction

Breast cancer that lacks expression of Estrogen receptors (ER), Progesterone receptors (PR), and HER 2 is labeled as triple negative. It accounts for ~ 15% of all breast cancer subtypes. Molecular studies have shown it to be Basal-like in the majority of cases.[1] Hereditary Breast cancer accounts for 10-15% of all breast cancer cases, BRCA1 and BRCA2 being the most common susceptibility genes.[2] These hereditary cancer patients usually present at an early age, and are mostly basal-like and triple-negative tumors[3] Lack of specific therapeutic targets makes it a poor risk group[4] Metastatic triple-negative breast cancer is an incurable disease where single agent or combination chemotherapy is

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Submission Date: 24-07-2023
1st Revision Date: 14-08-2023
Acceptance Date: 04-09-2023

traditionally being used to control symptoms and improve quality of life (QOL) of patients, depending upon disease burden.[5] Platinum-based therapies have proven their efficacy in metastatic triple-negative breast cancer.[6] Poly ADP ribose polymerase (PARP) inhibitors, a combination of Atezolizumab and nab Paclitaxel, Sacituzumab Govitecan, an antibody-drug conjugate are other treatment options[7] but unfortunately these drugs are expensive and not readily available making chemotherapeutic agents still most commonly used strategy.

Material and Method

The study was conducted in department of Medical Oncology and Radiotherapy from May 2019 to Februaray 2021 in which a total of 290 (145 in each arm) patients of metastatic TNBC were enrolled. A total of 290 patients (145 in each arm) of symptomatic metastatic triple-negative breast cancer, fulfilling inclu-sion criteria (ECOG 0-2, absence of symptomatic brain metastasis, Ejection fraction ≥ 55%, no psychiatric ill-ness, no grade ¾ neuropathy, no prior history of chest irradiation)) were randomly divided into 2 groups after taking informed consent. Clinicopathological characteristics were determined as pre-treatment evaluation using a questionnaire Group A received Adriamycin (60mg/m²) plus Cisplatin (75mg/m²) while Group B received Adriamycin (60mg/m²) plus Cyclophosphamide (600mg/m²) after baselines hematological and biochemistry profile. The chemotherapy cycle was repeated every 3 weeks for a total of 4 cycles, response was assessed using a contrast-enhanced CT scan after completion of therapy according to RECIST criteria version 1.01. National Cancer Institute Common Toxicity Criteria version 4.03 (CTCAE) was used to document toxicities at end of treatment. EORTC QLQ- C30 was used to determine health-related quality of life with a minimum decrease of ≥ 10 points considered significant. Data was entered and analyzed in SPSS (Statistical Package for Social Sciences) version 23. The quantitative variables like age were calculated by taking the mean and standard deviation. Qualitative variables like tumor response rate and dose-limiting toxicity were calculated by taking percentages and frequencies. Confounding factors like age and duration of illness were enrolled by stratification. Independent sample t-test was used for comparison between two groups with p value less than 0.05 taken as significant.

Results

A total of 290 patients (145 in each group) were enrolled in the study with an age range between 18-60 years. Mean age in Group A was 41.28±12.52 and in Group B it was 42.15±12.47 (p=0.554). Clinicopathological parameters were comparable in both groups. In group-A, 33(22.8%) had complete response, while 67(46.2%) had partial response followed by stable disease in 25 (17.2%) and progressive disease in 20(13.8%), while in group-B, 23(15.9%) had complete response, while 66 (45.5%) had partial response followed by stable disease in 41(28.3%) and progressive disease in 15 (10.3%), the difference was insignificant (p=0.094). At the end of treatment, more grade 3/4 neuropathy

Table 1: *Demographic characteristics in Groups.*

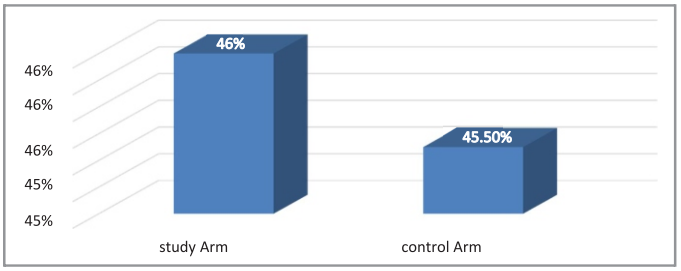
Demographic characteristics	Group A	Group B	P value
Age	41.28±12.52	42.15±12.47	0.554
Residence			
Rural	84	81	0.722
urban	81	64	
Marital status			
Married	143	2	1.0
Single	143	2	
Socio-economic status			
Lower(<20,000Pkr/M)	73	71	
Middle(20,000-50,000			0.687
Pkr/M)	62	67	
Upper(.50,000Pkr/M)	10	1	
Co-morbid illness			
No	116	118	
DM	15	14	0.902
HTN	11	11	
IHD	1	0	
Others	2	2	
Disease Characteristics			
Lymph Node Involvement			
Yes	129	119	
No	16	26	0.095
Sites Of Metastasis			
Lung	66	64	0.960
Liver	43	42	
Bones	34	36	
Others	2	3	
Family history of breast cancer			
Yes	39	33	0.415
No	106	112	
BreastCancer Morphology			
IDC	141	141	
ILC	2	2	1.0
Metaplastic carcinoma	2	2	

Table 2: *Comparison of Response between two study arms.*

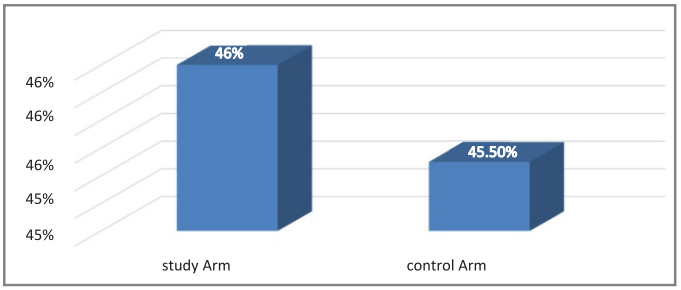
Response	Adriamycin plus Cisplatin		Adriamycin plus Cyclophosphamide	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
CR	33	22.8	23	15.9
PR	67	46.2	66	45.5
SD	25	17.2	41	28.3
PD	20	13.8	15	10.3

Table 2: *Comparison of toxicity between two groups:*

Toxicity	Adriamycin plus Cisplatin		Adriamycin plus Cyclophosphamide	
	Frequency (n) (Average/ cycle)	Percentage (%) (average/ cycle)	Frequency (n) (Average/ cycle)	Percentage (%) (average/ cycle)
Nausea	12.25	4.2	11.25	3.877
Vomiting	10.5	3.62	11.25	3.877
Diarrhea	2.75	0.94	2.75	0.94
Neutropenia	3.25	1.12	1	0.34
Neuropathy	5.25	1.8	0	0
Nephropathy	9.5	3.27	0	0



(p=0.004) and nephropathy (p=0.00007) were observed in the Cisplatin group but no difference in the quality



of life was noted between the two groups (p=0.540).

Figure 1: *Comparison of complete response between two*

Fig-2: *Comparison of complete response between two*

Discussion

Breast cancer is the common most malignancy affecting females of all ages with an estimated 271,270 new cases and 42,260 deaths in the USA, according to Cancer statistics 2019.[8] Breast cancer is classified traditionally on the basis of biomarkers, detected by Immunohistochemical staining, including the presence of Estrogen receptors (ER), Progesterone receptors (PR), and overexpression of Human epidermal growth factor receptor (HER2) the later if comes equivocal (+2) is confirmed by FISH (Fluorescence in situ hybridization). Recent advances in Gene expression profiling has led to new molecular classification of Breast cancer which include Luminal A, Luminal B, HER2 enriched, normal breast-like, and Basal-like.[9] Term triple negative Breast cancer (TNBC) encompasses a group of various types of breast cancer that share the common feature of lack of expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Overexpression of HER 2 Neu. Basal-like claudin-low and normal breast-like are the most common molecular subtypes that are seen in patients with TNBC. In literature, both terms Basal-like and TNBC are used as synonymous though gene expression analysis shows that in around 25% of cases, TNBC is not basal-like.[10] In early-stage TNBC, guidelines for surgery and Local Radiotherapy are the same as for other breast cancer subtypes. However, unlike other subtypes, these tumors are more sensitive to chemotherapy.[11] This chemo-sensitivity is particularly important in a Neo-adjuvant setting where patients get high pathological responses to standard chemotherapeutic agents. "TNBC paradox" is a unique feature of TNBC, where despite good clinical response to standard chemotherapy, the survival rates of these patients are poor. TNBC has shown particular sensitivity to platinum agents which relates to the high expression of BRCA gene mutations in these patients as carriers of these mutations have defective double-stranded DNA repair which exhibits response to DNA-damaging drugs.[12] A study published in "Annals of Oncology" in 2021, has shown improvement in pCR, with the addition of Carboplatin to neo-adjuvant chemotherapy in TNBC.[13] A meta-analysis has shown a 13% improvement in pCR with the addition of Platinum with taxane chemotherapy (p=0.0001) in early-stage disease and a statistically significant improvement in PFS in metastatic disease p=0.24.[13] Platinum drugs (Cisplatin or Carboplatin) are the preferred first-line agent to treat BRCA mutated metastatic triple negative Breast cancer while in patients who don't harbor such mutations, Platinum drugs are used in first or subsequent lines either as a single agent or in combination with other drugs depending upon symptom burden.[14] In our study, we

administered Doxorubicin which is the standard first-line chemotherapy in metastatic Breast cancer in combination with Cisplatin in patients who had symptomatic metastatic TNBC and compared its response with a combination of Doxorubicin and cyclophosphamide. From our literature search, we know that among our selected patient population, BRCA-mutated patients are the most suitable candidate for interventional drug combination but as this study is conducted in a public sector hospital in Pakistan where BRCA testing is not routinely done because of its cost and lack of facilities. So, we introduced Cisplatin along with Doxorubicin to see the response which in turn is a reflection of BRCA positivity in this population as there are high chances of this genetic mutation being present in those who responded. The results of our study showed that there is no statistically significant difference in response rates between the two arms with a high frequency of neuropathy and nephropathy observed in the intervention arm. Another limitation of this study is that we only checked for objective response rate, long term follow-up and analysis for survival aren't included in this study. Toxicity profile was comparable between two treatment groups with slightly more neuro toxicity and nephrotoxicity observed in cisplatin arm. However, quality of life which is an important parameter in the management of metastatic cancer was given due importance and it showed that there was no difference in the quality of life among the two patient groups.

Conclusion

There is no difference in response rates in both treatment arms however the use of Cisplatin with Adriamycin is associated with more toxicity making it inferior to the standard Adriamycin plus doxorubicin combination.

Conflict of Interest *None*

Source of Funding *None*

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Authors Contribution

YS: Conceptualization of Project
KAM: Data Collection
ZA: Literature Search
GWAM, KAM: Statistical Analysis
RA, ZA, NKAZ: Drafting, Revision
SY, RA: Writing of Manuscript