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Randomized Comparative Study of Neoadjuvant Chemotherapy in Locally Advanced and Metastatic Breast Cancer, 'FACVP' Vs 'ACT' Protocol

Dr. Md. Rafiqul Islam[1*], Dr. Md. Hanif Ulubbee[2], Dr. Hosne Ara Begum[2], Dr. Sharmin Billah[3], Dr. Mosfika Rahman[4], Dr. Md. Shahriar Kabir[5], Dr. Sharmin Sultana[6], Dr. Nazma Azim[7]

[1]Assistant Professor, Department of Medical Oncology, National Institute of Cancer Research & Hospital (NICRH) Dhaka, Bangladesh
[2]Assistant Professor, Department of Radiation Oncology, National Institute of Cancer Research & Hospital, (NICRH) Dhaka, Bangladesh
[3]Registrar, Department of Radiation Oncology, National Institute of Cancer Research & Hospital (NICRH) Dhaka, Bangladesh
[4]Assistant Registrar, Department of Medical Oncology, National Institute of Cancer Research & Hospital, Dhaka, Bangladesh
[5]OSD, DGHs, Medical Officer, Department of Medical Oncology, National Institute of Cancer Research Hospital (NICRH), Dhaka, Bangladesh
[6]Principal Medical Physicist, Department of Radiation Oncology, National Institute of Cancer Research & Hospital, (NICRH) Dhaka, Bangladesh
[7]Programmer, Department of Medical Information System (MIS), National Institute of Cancer Research & Hospital, (NICRH) Dhaka, Bangladesh

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***Corresponding author:** Dr. Md. Rafiqul Islam
Assistant Professor, Department of Medical Oncology, National Institute of Cancer Research & Hospital (NICRH) Dhaka, Bangladesh

Abstract

Original Research Article

Background: Breast cancer is one of the most frequently diagnosed cancer of Bangladeshi women and presents comparatively at late stage of their diseases. Neoadjuvant chemotherapy has been recommended as the primary treatment of choice in locally advanced and metastatic breast cancers. ***Objective:*** To assess the clinical response, comparison of responses, toxic effects of two schedules of neo-adjuvant chemotherapy randomly applied in patients with locally advanced and metastatic breast cancer. ***Material & Methods:*** This randomized control trial study was carried out in the Department of Medical Oncology, National Institute of Cancer Research & Hospital, Dhaka, Bangladesh from July 2009 to June 2010. The study cases were locally advanced and metastatic breast cancer. Most of the cases were histological proved infiltrating duct cell carcinomas of both sexes and age was between 20-60 years. The study was comprised of two arms; ACT arm; -combination of three drugs such as Adriamycine, Cyclophoshphamide, Paclitaxel and FACVP arm; - combination of five drugs such as 5- Fluorouracil, Adriamycine, Cyclophosphamide, Vincristine, Prednisolone. A total of 70 patients were enrolled in this study of which 35 patients were included in the ACT arm and the rest 35 patients in FACVP arm. Total six cycles of chemotherapy were given in each patient at 21 days' interval. After two cycles, each patient was evaluated clinically to measure clinical response. All the data were compiled and analyzed by SPSS version 12.0. ***Results:*** All the cases were locally advanced and have metastatic disease and almost all were (97%) with axillary lymph node involvement. Left and right breast involvement was (54.3%) and (46.7%) in FACVP arms respectively. Left and right breast involvement was (51.4%) and (48.6%) in ACT arm respectively. Two patients were with both breast involvements in ACT arm. Characteristics of the patients such as body build, age, stage, performance status, social status were more or less equal in both groups. There was only one male patient who was included in ACT group. After completion of neoadjuvant chemotherapy, complete response was observed 40% and 37.1% in ACT and FACVP arm respectively. Partial response was observed 51,4% and 45.7%, in FACVP and ACT arm respectively. Stable disease was observing d 8.6% and 2.9% in FACVP and ACT arm respectively. Progressive disease was observed 11.4% and 2.9% in ACT and FACVP arm respectively. This result was not significant. Regarding toxicities, vomiting was observed more in FACVP arm than ACT arm, which is statistically significant. Arthralgia was observed more in ACT arm than FACVP arm which is statistically significant Other toxicities such as nausea, oral candidiasis and alopecia are more or less equal in both arm. ***Conclusion:*** In locally advanced and metastatic breast cancer the clinical response with neoadjuvant FACVP chemotherapy is equivalent to that of neoadjuvant ACT chemotherapy.

Keyword: Breast cancer, Neoadjuvant chemotherapy, ACT arm, Paclitaxel and FACVP arm, Adriamycine, Cyclophoshphamide, Fluorouracil, Adriamycine, Cyclophosphamide, Vincristine, Prednisolone.

INTRODUCTION

Breast cancer is the most common cancer of developed countries. In Bangladesh it is the second common cancer comprised of 12.3% of all cancer. Among the top ten cancers it ranks second position in female after cervical cancer [1]. In our country breast cancer patient usually present in an advanced stage due to poverty, ignorance, and lack of screening facilities for early detection of breast cancer. Locally advanced breast cancer is defined by American Joint Committee on Cancer (AJCC) staging criteria 2003 as: Tumor size greater than 5 cm with clinically or pathologically positive axillary lymph nodes; tumor of any size with direct extension to ribs, intercostal muscle, or skin; edema (including peau d' orange) or ulceration of the skin of the breast or satellite nodule confined to the same breast; inflammatory carcinoma (T4d); metastases to ipsilateral axillary lymph nodes fixed to one another or to other structure; metastases to the ipsilateral internal mammary lymph nodes; or metastases to the ipsilateral supraclavicular lymph nodes. When various organ involved in addition to primary tumor, it is regarded as metastatic disease. The role of neoadjuvant chemotherapy (NACT) for patient with locally advanced breast cancer (LABC) is now becoming established since 1980 [2]. The risk factors for breast cancer in women are well documented which includes age greater than 50 years, personal or family history of breast cancer, nulliparous, or first child after 30 years of age. The most important risk factor is age at first birth and nulliparity, higher socioeconomic status, and family history. Genetic linkage study has led to discovery of genetic mutation in two tumor suppressor gene BRCA-1 & BRCA-2 located to chromosome 17 & 13 respectively. Additional factor that increases breast cancer risk are early menarchy, late menopause, birth of first child after thirty years, oral contraceptive pill. It means prolong exposure to female hormone which increases the risk of breast cancer. Multiple pregnancies, breast feeding and physical activity is probably has got some protective role. Management of breast cancer is through multi modal approach which consists of surgery, chemotherapy, radiotherapy and hormone therapy. Mastectomy is simple mastectomy, Modified radical mastectomy and radical mastectomy. In breast conserving surgery only a part of the affected breast is removed. Lumpectomy removes only the breast lump and a surrounding margin of normal tissue. Partial mastectomy or quadrantectomy removes more breast tissue than a lumpectomy. Independently of what type of surgery is performed, these techniques can be accompanied by axillary lymph node drainage, which may cause upper limb lymph edema [3]. Radiation therapy remains an important component of the management of breast cancer. Radiation therapy after mastectomy was routinely carried out in patient with node positive disease and after breast conserving surgery. Radiation therapy reduced the local recurrence and improved the survival. Neo-adjuvant chemotherapy reduces the primary bulk disease, micro and macro metastasis. Various combination chemotherapy is available. They are 'FAC' (5-Fluorouracil, Adriamycin, Cyclophosphamide), 'FACVP' (5-Flurouracil, Adriamycin, Cyclophosphamide, Vincristin, Prednisolon), 'ATC' (Adriamycin, Cyclophosphamide, Paclitaxel), 'FEC' (5- Fluorouracil, Epirubicin, Cyclophosphamide) 'AC' (Adriamycin, Cyclophosphamide), 'AT' (Adriamycin, Paclitaxel), 'CMF' (Cyclophosphamide, Methotrexate, 5-Fluorouracil), 'PC' (Paclitaxel, Carboplatin); 'DAC' (Docetaxel, Adriamycin, Carboplatin). Neoadjuvant chemotherapy was undertaken with the aim of shrinking the tumor in patients who are not candidates for primary surgery, and in the hope of allowing greater conservation of the breast with locally advanced breast cancer. Who achieve complete clinical response with the induction of neoadjuvant chemotherapy was at least to some extent predictive of long term survival benefit. The use of neoadjuvant approach led to a significant or near significant increase in the proportion of patients disease-free at 5 years [4]. Neoadjuvant therapy increases the likelihood of more breast conservation surgery. Surgery usually performed as part of breast cancer treatment includes mastectomies and breast conserving surgery. Chemotherapy has got acute, sub-acute and long term toxicities. Acute toxicities are vomiting, diarrhea, fever etc. Sub-acute toxicities are alopecia hemorrhagic cystitis, hypertension, edema and psychological abnormalities. Long term toxicities may be cardiac, second malignancy and psycho neurological. Nausea and vomiting can usually be minimized by pre-hydration and anti-emetic drug. To minimize the side effects sometimes the dose of the drug is decreased depending on the age, sex, co-morbid condition, extent of the disease and performance status of the patient. Neo-adjuvant therapy is the treatment given before primary therapy. A woman may receive neo- adjuvant chemotherapy for breast cancer to shrink a tumor that is inoperable in its current state, so it can be surgically removed [5]. A woman whose tumor can be removed by mastectomy may instead receive neo-adjuvant therapy to shrink the tumor enough to allow breast-conserving surgery [6]. Neo-adjuvant chemotherapy is given in the same manner as adjuvant chemotherapy. Clinical trials have been conducted to learn how to treat breast cancer more effectively. Clinical trials allow researchers to observe the effectiveness of new treatments in comparison with standard ones, as well as to compare the side effects of the treatments.[5] In this randomized comparative study neoadjuvant chemotherapy was used in locally advanced and metastatic breast cancer following `FACVP' vs `ACT' protocol.

OBJECTIVES

General Objectives

To compare the response of 'FACVP' and 'ACT' chemotherapy in locally advanced and metastatic breast carcinoma.

Specific Objectives

- To determine the clinical response of primary tumor, regional lymph node and other metastasis sites.
- Response of primary tumor
- To compare the response of primary tumor, regional lymph node and others between two arms.
- To observe the toxic effect of chemotherapy and compare between two arms.

MATERIALS AND METHODS

Type of Study

This was a randomized control trial (RCT) study.

Place of Study

This study was carried out in the Department of Medical Oncology at National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka.

Period of Study

This study was carried out during the period from July 2009 to June 2010 for one year.

Study Population

All patients with a age between (20-60) years of both sex presented with histological proven locally advanced and metastatic breast cancer, with a performance status within (0-02) scale attending in the Department of Medical Oncology at National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka were taken as study population

Sample Size

A total of 70 patients were enrolled in this study and they were divided into two groups. Each group contained 35 patients (35 in FACVP & 35 in ACT group). All were suffering from locally advanced and metastatic breast cancer.

Sampling Technique

The sampling technique was consecutive random sampling and this purposive sampling technique was used as per inclusion and exclusion criteria.

Selection Criteria of Study Population

Inclusion Criteria

- Histologically proven locally advanced and metastatic breast cancer.
- Age of the patient between 20 - 60 years
- Performance status within (0 - 02) scale
- No history of prior surgery, chemotherapy or radiotherapy
- Participants who had given the consent and willing to comply with the study procedure were included.

Exclusion Criteria

- Previously treated i.e., surgery, Chemotherapy and Radiotherapy
- Age below 20 years and more than 60 years
- Performance status more than (02) scale according to WHO
- Impaired Kidney and liver function test i.e.- serum creatinine >2mg/dl, SGPT>3 times of normal values
- Poor cardiac status (in echocardiography- ejection fraction is less than 45%)
- Patients who refused to give consent to take medication as advised
- Patients or attendants unwilling to take part in the study

Study Design

In this single centered randomized control study, randomization was done accordingly. On day 1 of each cycles, eligible patients received either ACT (50mg of doxorubicin per square meter of body surface area in an intravenous infusion for 15 minutes, followed by 600mg of cyclophosphamide per square meter administered intravenously for 10 to 15 minutes. On day 2 of each 175 mg of paclitaxel per square meter of body surface area in an intravenous infusion for 1 hour). or FACVP (50 mg of doxorubicin per meter square followed by 500 mg of 5-fluorouracil per meter square, cyclophosphamide 600mg per meter square followed by vincristin 1.4 mg per meter square each as an intravenous for 15 minutes and oral prednisolon 40 mg per meter square on day (1-5) was given in each cycle.

Study Procedure

This was a randomized control comparative study between two different group of chemotherapy to compare and to determine the role of neo adjuvant chemotherapy in patient of locally advanced and metastatic breast cancer. Patient were recruited from outdoor and indoor department of National Institute of Cancer Research and Hospital, Mohakhali, Dhaka. After selection the patient came to medical oncology department for receiving treatment and used to come 21days apart after each cycle for consecutive six cycles in order to complete the treatment. In between each cycle usually after 10 day's complete blood count, liver function test, renal function test was done to see and to compare the result with the previous report as well as to record the toxicities in the follow up sheet as mentioned by the patient. Blood transfusion, control of infection and toxicities management was given accordingly. In this period patient and investigator made evaluation of

treatment effectiveness at three weekly intervals during treatment and follow up phase. Improvement was observed on primary breast tumor and axillary lymph node and response was categorized accordingly.

Steps of the Study Procedure

1. Step-I: Selection of the patient; A questioner was designed and clinical history, laboratory investigation result was recorded. On the basis of clinical history, physical finding and laboratory result patient were selected.
2. Step-II: Consent taking after explanation- consent was taken from the selected patient after full explanation of the procedure of our study, if anybody did not give consent then he or she was excluded from the study.
3. Step-III: History taking fill-up of questionnaire subjects who signed the informed consent form was included in the study. A questionnaire was filled up from the selected patient by a co-investigator. The questionnaire was pre-tested at first and finalized.
4. Step-IV: Identification of breast cancer patient- all patient having a histopathological diagnosis of breast cancer categorized as locally advanced and metastatic breast cancer by the questionnaire according to inclusion and exclusion criteria.
5. Step-V: Randomization of patient either ACT or FACVP group subjects were randomized tc receive either ACT or FACVP therapy.
6. Step-VI: Dispensing of medication- before giving chemotherapy in each group premedication was given with dexamethason, ranitidine antiemetic and chlorpheniramine. All the drugs were given intravenously. In case of ACT therapy additional premedication was started one day before the start of chemotherapy with dexamethasone, ranitidine, and antihistamine. All the drugs were given orally. Chemotherapy drug were diluted with normal saline and then given in intravenous infusion slowly with burette set. Patient was observed for five minutes initially for any unwanted reaction. If any reaction develops such as rash, flushing, respiratory distress, it was controlled by injection hydrocortisone injection chlorpheniramine and necessary therapy. There was 21 days' gap between each cycle of chemotherapy.
7. Step-VII: Follow up; Dispensing of medication and follow-up continued simultaneously. Initially it was every 3 weeks up to18 weeks and then continued monthly intervals for one year.
8. Step-VIII: Compilation of data. after completion of neoadjuvant chemotherapy and necessary follow-up, data were compiled and was analyzed to determine the role of neoadjuvant chemotherapy and to compare the response and toxicities between two groups in patient with locally advanced and metastatic breast cancer.
9. Step-IX: Analysis of data. the analysis of data may be broadly classified into the following heads;

Statistical Analysis

All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using SPSS (Statistical Package for Social Sciences) for windows version 12.0. 95% confidence limit was taken. Probability value <0.05 was considered as level of significance.

Ethical Implications

Prior to the commencement of this study, the research protocol was approved by the ethical committee of National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka. The study was enrolled the population of both sexes who were diagnosed as breast carcinoma and took cancer chemotherapy. There was threat or risk for study population. It was not disclosed their privacy.

RESULT AND OBSERVATION

A total number of 75 patients within 20-60 years of age of both sexes were enrolled in this study of which 38 patients were treated with ACT therapy and the rest 37 patients were taken FACVP chemotherapy who were presented with histological proven locally advanced and metastatic breast cancer, with a performance status within (0-02) scale attending at the Department of Medical Oncology at National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka. Three patients in ACT group and two patients in FACVP group were dropped out due to non-compliance and poverty. So, finally 35 patients in each group were enrolled in the study. There was only one male patient in ACT group and none in FACVP group. So there was frank predominance of female patient (98.57%) In ACT group majorities of patients were in the age group of 31-40 years (42.9%). Response of chemotherapy between two groups was observed over primary breast lump. Complete response was observed in 14(40.0%) cases and 13(37.1%) cases in ACT and FACVP group respectively, which was almost equivalent between two groups. Partial response was slightly more in FACVP group 18(51.4%) in comparison to 16(45.7%) cases in ACT group. Progressive diseases was more 4(11.4%) in ACT group in comparison to 1(2.9%) in FACVP group respectively. Only complete response was slightly more in ACT group. Which were (2.9%) less in FACVP group? This difference is not statistically significant.

Significant improvement was observed on axillary lymph node before and after chemotherapy in both groups. After treatment axillary lymph node became clinically non-palpable in 14(41.2%) cases and 15(44.1%) cases in ACT and FACVP groups respectively. So, the FACVP chemotherapy showed a little better response over lymph node than ACT chemotherapy. Toxicities profile between two groups was observed after chemotherapy. Vomiting is found in 16(45.7%) cases and 26(74.3%) cases in ACT and FACVP groups respectively, which is statistically significant. Diarrhea is observed in 22(62.9%) cases and 18(51.4%) cases in ACT and FACVP groups respectively. The difference was not statistically significant. Oral candidiasis is detected in 26(74.3%) case and 23(65.7%) cases in ACT and FACVP groups respectively. The difference was not statistically significant. Alopecia is found in 27(77.1%) cases and 31(88.6%) cases in ACT and FACVP groups respectively. The difference was not statistically significant.

Table I: Distribution of age by groups (N=70)

Age (in year)	Groups		p value
	ACT	FACVP	
20-30 yrs.	3 (8.6)	5 (14.3)	0.471
31-40 yrs.	15 (42.9)	16 (45.7)	
41-50 yrs.	11 (31.4)	12 (34.3)	
51-60 yrs.	6 (17.1)	2 (5.7)	
Mean ± SD	42.45 ± 8.99	40.97 ± 8.13	

Table I showed the distribution of the study population according to the age by groups. In ACT group majority were in age group of 31-40 years which was 15(42.9%) cases followed by 41-50 year's age group, 51-60 years and 20-30 years which were11(31.4%) cases, 6(17.1%) cases and 3 (8.6%) cases respectively. In 35 patients in FACVP group majority were in the age group of 31-40 years which was 16(45.7%) cases followed by 41-50 years, 51-60 years and 20- 30 years which were 12(34.3%) cases, 2(5.7%) cases and 5(14.3) cases respectively. The mean age in ACT and FACVP groups were 42.45 ± 8.99 and 40.97±8.13 years respectively. The difference was not statistically significant.

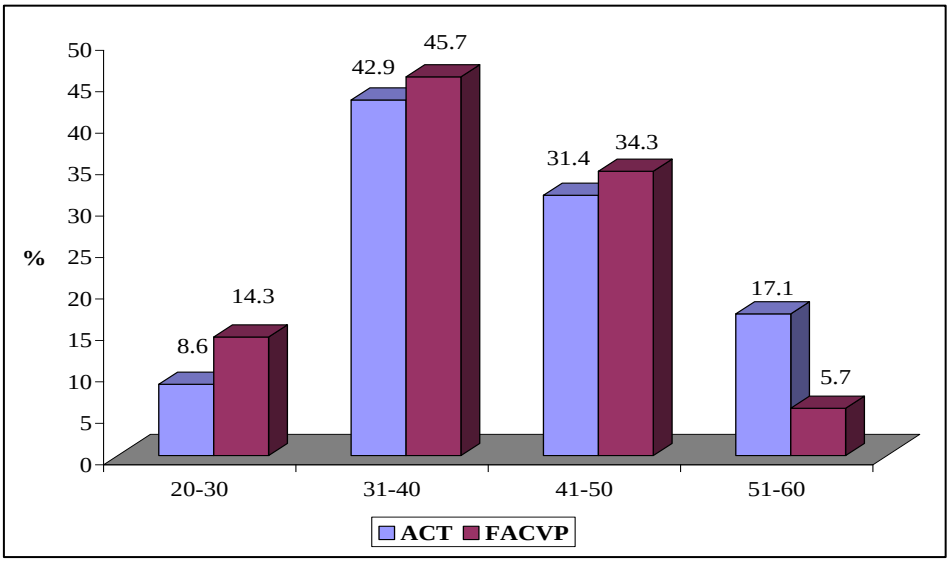

Figure 1: Bar diagram of age by groups

Table II: Distribution of risk factors by groups

Risk factors	Groups		p value
	ACT	FACVP	
Oral contraceptive	18(51.4)	21(60.0)	0.470
Family H/O breast cancer	1(2.9)	2(5.7)	0.999
Past H/O breast disease	1(2.9)	0(0.0)	0.999

Table II showed the distribution of risk factors by groups. Oral contraceptives are taken in highest number both in ACT group and FACVP group which were 18(51.4%) and 21(60.0%) cases respectively. Family H/O breast cancer was 1(2.9%) case and 2(5.7%) cases in ACT group and FACVP group

respectively. Past H/O breast disease were found in only ACT group which was 1(2.9%).

Table III: Distribution of side of lump by groups (N=70)

Side of lump	Groups		p value
	ACT	FACVP	
Right	17(48.6)	18(51.42%)	
Left	16(45.7)	19(54.3)	0.319
Both	2(5.7)	0(0.0)	

Table III showed the distribution of side of lump by groups. Right sided lump was found in 17(48.6%) cases and 18 (51.42%) cases in ACT group and FACVP group respectively. Left sided lump was found in 16(45.7%) cases and 19 (54.3%) cases in ACT group and FACVP group respectively. Only 2(5.7%) cases were found in both sides. This difference is not statistically significant.

Table IV: Distribution of general examination by groups (N=70)

General examination	Groups		p value
	ACT	FACVP	
Appearance			
Good	21(60.0)	13(37.1)	0.056
Ill Looking	14(40.0)	22(62.9)	
Body build			
Good	9(25.7)	5(14.3)	0.077
Average	21(60.0)	17(48.6)	
Below Average	5(14.3)	13(37.1)	
Nutrition			
Good	9(25.7)	7(21.2)	0.218
Average	21(60.0)	16(48.5)	
Below Average	5(14.3)	10(30.3)	
Anemia	33(94.3)	34(97.1)	0.999
Jaundice	1(2.9)	1(2.9)	0.999
Edema	0(.0)	1(2.9)	0.999
Dehydration	14(40.0)	19(54.3)	0.231
Palpable neck node	2(5.7)	3(8.6)	0.999

Table IV showed the distribution of general examination by groups. Appearance good is found more in ACT group than FACVP which are 21(60.0%) cases and 13(37.1%) cases respectively. Appearance ill looking was found more in FACVP group than ACT group which are 22(62.9%) cases and 14(40.0%) cases respectively. The difference was significant. Body build is good in 9(25.7%) cases and 5(14.3%) cases in ACT group than FACVP respectively. Body build is average in 21(60.0) cases and 17(48.6%) cases in ACT group than FACVP respectively. Body build is below average in 21(60.0) cases and 17(48.6%) cases in ACT group than FACVP respectively. Anemia was found in 34(97.1%) cases and 33 (94.3%) cases in ACT group than FACVP groups respectively. Jaundice was present in 1(2.9%) case in both ACT group than FACVP groups. Edema is present only in 1(2.9%) case in FACVP group. Dehydration is present in 14(40.0%) cases and 19(54.3%) cases in ACT group than FACVP groups respectively. Palpable neck node was found in 2(5.7%) and 3(8.6%) cases in ACT group than FACVP groups respectively.

Table V: Distribution of clinical responses by groups (N=70)

Responses	Groups		Total	p value
	ACT	FACVP		
Complete response	14(40.0)	13 (37.1)	27 (38.6)	0.806
Partial response	16 (45.7)	18 (51.4)	34 (48.6)	0.632
Stable Disease	1 (2.9)	3 (8.6)	4 (5.7)	0.614
Progressive Diseases	4 (11.4)	1 (2.9)	5 (7.1)	0.356

Table V showed the distribution of response by groups. Complete response was found in 14(40.0%) cases and 13(37.1%) cases in ACT and FACVP groups respectively. Partial response was observed in 16(45.7%) cases and 18(51.4%) cases in ACT and FACVP groups respectively. Disease was stable in 1(2.9%) case and 3(8.6%) cases in ACT and FACVP groups respectively. Progressive Diseases is found in

4(11.4%) cases and 1(2.9%) case in ACT and FACVP groups respectively. Only complete response is slightly more in ACT group (40.0%) than FACVP group which is (37.1%) only. But partial response was more in FACVP (51.4%) than ACT group which is (45.7%). Progressive diseases are only 2.9% in FACVP group which was more (11.4%) in ACT group. Stable diseases are more in FACVP group (8.6%) than ACT group which is only 2.9%. But the difference is not statistically significant.

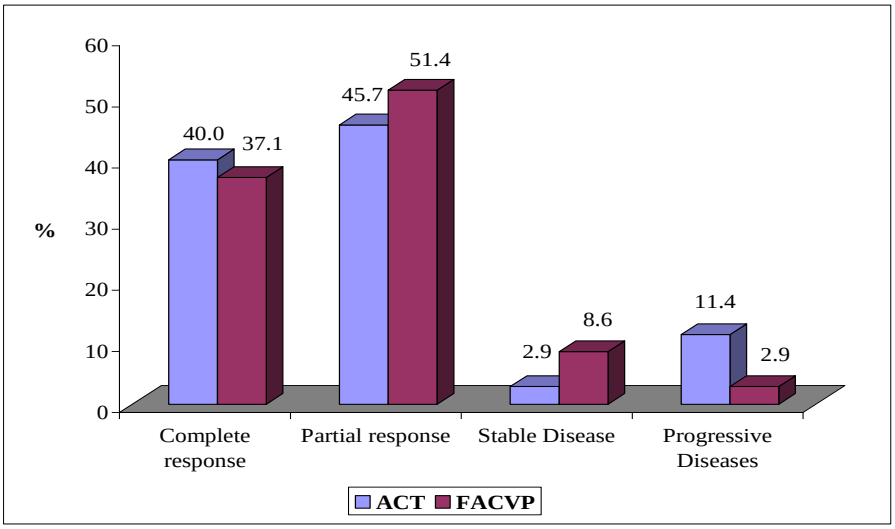

Figure 2: Bar diagram of study population according to response by group

Buzdar *et al*., (1988) [7] were found a similar result and mentioned that a combination of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) has been evaluated as adjuvant therapy for breast cancer since 1974 and showed a significant prolongation of the disease-free interval and survival of patients with Stage II or III breast cancer, irrespective of menopausal status. Buzdar *et al*., (1988) [7] also added that two non-myelosuppressive drugs were added to the FAC regimen (FACVP). Both drugs produced 15% to 20% response in patients with advanced breast cancer.

Table VI: Distribution of axillary lymph node status by groups

Axillary lymph node palpable	Groups		p value
	ACT	FACVP	
Before treatment	34 (97.1)	34 (97.1)	0.806
After treatment			
Palpable	20 (58.8)	19 (55.9)	
Not palpable	14 (41.2)	15 (44.1)	

Table VI shows the distribution of axillary lymph node by groups. Before treatment axillary lymph node was palpable in 34(97.1%) cases and 34(97.1%) cases in ACT and FACVP groups respectively. After treatment axillary lymph node became clinically not palpable in 14(41.2%) cases and 15(44.1%) cases in ACT and FACVP groups respectively. So, the FACVP chemotherapy produce a little better response over axillary node than ACT chemotherapy. But still the difference was not statistically significant.

Table VII: Distribution of toxicities by groups

Toxicities	Groups		p value
	ACT	FACVP	
Vomiting	16 (45.7)	26 (74.3)	0.015
Nausea	22 (62.9)	18 (51.4)	0.334
Oral candidiasis	26 (74.3)	23 (65.7)	0.434
Alopecia	27 (77.1)	31 (88.6)	0.205
Arthralgia	24(68.6)	15(42.8)	0.017.

Table VII showed the distribution of toxicities by groups. Vomiting was found in 16(45.7%) cases and 26(74.3%) cases in ACT and FACVP groups respectively. The difference was statistically significant. Nausea was observed in 22(62.9%) cases and 18(51.4%) cases in ACT and FACVP groups respectively. The difference was not statistically significant. Oral candidiasis was detected in 26(74.3%)

case and 23(65.7%) cases in ACT and FACVP groups respectively. The difference was not statistically significant. Alopecia was found in 27(77.1%) cases and 31(88.6%) case in ACT and FACVP groups respectively. The difference was not statistically significant. Arthralgia was noted in 24(68.57%) cases and 15(42.85%) cases in ACT and FACVP group respectively. The difference was statistically significant.

Table VIII: Distribution of toxicities grading by group

FACVP Group

Toxicities	Grade 0	Grade I	Grade II	Grade III	Grade IV
Vomiting	09(25.7%)	06(17.14%)	11(31.42%)	05(14.28%)	04(11.42%)
Nausea	17(48.57%)	07(20.00%)	05(17.14%)	04(11.42%)	02(5.71%)
Alopecia	04(11.42%)	20(57.14%)	11(31.43%)	-	-
Oral candidiasis	12(34.28%)	07(20.00%)	10 (28.57%)	04(11.42%)	02(5.71%)
Arthralgia	20(57.15%)	09(25.71%)	03(8.57%)	02(5.71%)	01(2.86%)

ACT Group

Toxicities	Grade 0	Grade I	Grade II	Grade III	Grade IV
Vomiting	19(54.28%)	06(17.14%)	05(14.28%)	03((8.54%)	02 (5,71%)
Nausea	13(37.17%)	09(25.71%)	0617.14%)	05(14 28%)	02(5.71%)
Alopecia	08(22.86%)	1(52.86%)	12(34.28%)	-	-
Oralcandidiasis	09(25.71%)	08(22.85%)	09(25.71%)	06(17.14%)	03(8.54%)
Arthralgia	11(31.43%)	08(22,85%)	07(20.00%)	05(14.28%)	04(11.42%)

Table VIII: showing distribution of toxicities grading by Group-Vomiting was more pronounced in FACVP arm.74.3% patient developed vomiting and 25.7% of patient had no vomiting after chemotherapy. In 74,3% who had vomiting maximum 31.42% are in grade II and 11.42% are in grade IV toxicities. grade IV toxicities requiring intravenous medication. In contrast in ACT arm maximum 54.28% patient had no vomiting. Rest 45.7% developed vomiting in which maximum 17.14% belongs to grade I and 5.71% shows grade IV toxicities. Nausea is less observed in FACVP arm. In FACVP arm 48.57% had no nausea in comparison to 37.17% in ACT arm. Among the patient who developed nausea maximum 20.0% belongs to grade I in FACVP arm and 25.71% belongs to ACT arm. Grade III toxicities occur more in ACT arm which was 14.28 % in comparison to 11.42% in FACVP arm. Alopecia was more observed in FACVP arm. In FACVP arm 11.42% patient developed no alopecia in comparison to 22.86% in ACT arm. Among the patient who developed alopecia maximum 57.14% belongs to grade I in FACVP arm and 52.86% belongs to grade I in ACT arm respectively. Grade II toxicities occur more in ACT arm which was 34.28% in comparison to 31.43% FACVP arm. Oral candidiasis was more observed in ACT arm. In ACT arm 25.71% and in FACVP arm 34.28% patient developed no oral candidiasis. Among the patient who developed oral candidiasis maximum 28.57% patient belongs to grade II in FACVP arm and 25.715 patients belongs to grade II in ACT arm. Grade IV toxicities occur more in ACT arm, which was 8.54% patient in comparison to 5.71% patient in FACVP arm. Arthalgia is more observed in ACT arm. About 68.54% developed arthalgia in ACT arm in comparison to only 42.85% in FACVP arm. 31.43% in ACT arm and 57.15% cases in FACVP arm developed grade 0 toxicities or no arthalgia. Grade I toxicity is more in FACVP arm which is 25.71% and grade IV toxicity is more observed in ACT arm which is 11.42%. Arthalgia was more in ACT arm probably due to incorporation of taxens in ACT arm.

Table IX: showing response according to Body Mass Index (BMI) by group

ACT Therapy

BMI	No	CR	PR	SD	PD
<18.5	05	1(7.14%)	2(12, 50%)	0(0%)	2(50%)
18.5-24.9	22	10(71, 42%)	11(68.75%)	1(100%)	0(0%)
25.0-29.9	07	3(21.42%)	3(18.75%)	0(00%)	1(25%)
>30	01	0(0.0%)	0(0.0%)	0(0.0%)	1(25%)

FACVP Therapy

BMI	No	CR	PR	SD	PD
<18.5	04	2(15.38%)	2(11.11%)	0(0%)	0(0.0)
18.5-24.9	24	9(69.23%)	12(66.66%)	3(75%)	0(0.0)
25.0-29.9	07	1(7.69%)	4(22.22%)	1(25%)	1(100%)
>30	01	1(7.69%)	0(0.0%)	0(0.0%)	0(0.0%)

Table IX: showed response according to body mass index by group- among the responses 71.42% in ACT and 69.25% in FACVP, complete response occurred within BMI range between 18.5-24.9 which is normal for age and sex indicating good nutrition and good body build. Also partial response was observed more in the same group which was 68.75% in ACT and 66.66 in FAC VP arm respectively. Progressive disease was observed about 50% &25% with the BMI range between <18 & 25-29.9 respectively in ACT group indicating that response was not satisfactory in the under nutrition, & obese group. In comparison in FACVP group progressive disease was 100% in BMI ranging 25-29.9 indicating obese patient. So body mass index as an indicator of good nutrition was a good predictor of chemotherapy response.

Table X: Stage grouping of the study population

Stage	No of Patients		Total No		Total Percentage(%)
	ACT	FACVP	%	Locally Advanced	
IIA	1	1	2.85	62	88.5
IIB	5	5	12.85		
IIIA	18	16	48.57		
IIIB	3	7	14.28		
IIIC	4	3	10.0		
				Metastatic Disease	
IV	4	4	11.43	8	11.43

Table X: Among the total study population in both group majority of the patient are in locally advanced group. It was about 88.57% and only about 11.43% patients are in stage IV metastatic carcinoma of breast. Within the locally advanced category, a total of 48.57% patient was in stage IIIA in both groups.

Table XI According to histopathological finding the patient distribution by group (N=70)

	Groups		
Histopathology	**ACT**	**FACVP**	**Total**
Duct Cell Carcinoma	34(97.14)	33(94.28)	67(95.72)
Inflammatory carcinoma	1 (2.86)	0(0.0)	1(1.43)
Medullary carcinoma	0(0.0)	1(2.86)	1(1.43)
Lobular carcinoma	0 (0.0)	1(2.86)	1(1.43)

Table XI: In this study out of 70 patients, 67(95.72 %) have duct cell carcinoma and only 4.28% are others. Among the others inflammatory carcinoma was 2.86% which belongs to ACT arm. Medulllary carcinoma and lobular carcinoma together constitute 5.72% of carcinoma which belongs to FACVP arm.

Table XII: Mean ± SD of investigations variables by follow up

Investigations variables	Before	After	p value
Hb			
ACT	10.81 ± 0.97	10.31 ± 1.00	0.028
FACVP	10.66 ± 1.24	10.04 ± 1.08	0.027
TC of WBC			
ACT	8390.54 ± 2483.11	10020.00 ± 16638.05	0.577
FACVP	13952.86 ± 22223.61	7722.86 ± 1998.69	0.105

Table XII showed the mean of investigations variables by follow up. The mean hemoglobin concentration is 10.81 ±0.97 and 10.31±1.00 in the ACT group in before and after the treatment which is statistically significant. The mean hemoglobin concentration is 10.66±1.24 and 10.04±1.08 in the FACVP group in before and after the treatment which is statistically significant. The mean total count of WBC is 8390.54±2483.11 and 10020.00±16638.05 in ACT group in before and after the treatment respectively which is statistically not significant. The mean total count of WBC is 13952.86±22223.61 and 7722.86±1998.69 in FACVP group in before and after the treatment respectively which was not statistically significant.

Table XIII: Mean ± SD of investigations variables by follow up

Investigations variables	Before	After	p value
Platelet			
ACT	230634.86 ± 77914.50	220257.1 ± 74237.83	0.464
FACVP	228657.14 ± 44283.81	228485.71 ± 40962.23	0.987
ESR			
ACT	64.57 ± 33.96	39.56 ± 19.30	0.001
FACVP	48.11 ± 25.37	56.20 ± 24.29	0.066

Table XIII showed the mean of investigations variables by follow up. The mean Platelet was 230634.86 ± 77914.50 and 220257.1±74237.83 in ACT group in before and after the treatment respectively which is not statistically significant. The mean Platelet was 228657.14±44283.81 and 228485.71±40962.23 in the FACVP group in before and after the treatment which was not statistically significant. The mean ESR is 64.57±33.96 and 39.56±19.30 in ACT group in before and after the treatment respectively which was statistically significant. The mean ESR is 48.11±25.37 and 56.20±24.29 in FACVP group in before and after the treatment respectively which was statistically significant.

Table XIV: Mean ± SD of investigations variables by follow up

Investigations variables	Before	After	p value
SGPT			
ACT	26.26 ± 6.14	40.43 ± 50.22	0.112
FACVP	29.23 ± 6.66	30.88 ± 8.00	0.224
Alkaline phosphates			
ACT	158.62 ± 37.00	193.54 ± 112.66	0.076
FACVP	165.01 ± 22.83	170.84 ± 21.09	0.238
Bilirubin			
ACT	0.58 ± 0.13	0.54 ± 0.12	0.197
FACVP	0.56 ± 0.10	0.63 ± 0.16	0.031

Table XIV: showed the mean of investigations variables by follow up. The mean SGPT was 26.26±6.14 and 40.43±50.22 in ACT group in before and after the treatment respectively which is not statistically significant. The mean SGPT is 29.23±6.66 and 30.88 ± 8.00 in the FACVP group before and after the treatment which was not statistically significant. The mean alkaline phosphates are 158.62±37.00 and 193.54±112.66 in ACT group in before and after the treatment respectively which was not statistically significant. The mean alkaline phosphates are 165.01±22.83 and 170.84±21.09 in FACVP group in before and after the treatment respectively which is not statistically significant. The mean bilirubin was 0.58±0.13 and 0.54±0.12 in ACT group in before and after the treatment respectively which was not statistically significant (p=0.197). The mean bilirubin is 0.56±0.10 and 0.63±0.16 in FACVP group in before and after the treatment respectively which was statistically significant.

DISCUSSION

In the present study, 70 patients of locally advanced breast cancer with or without metastasis were treated by neoadjuvant chemotherapy by two different schedules; 35 patients by three drugs combination (ACT) and 35 by five drugs combination (FACVP). In ACT arm, over all response was 85.7%; of them complete clinical response was observed in 40% and in FACVP arm overall response was 88.5% and complete response 37.1%. Shein T *et al*., showed [8] that overall neo-adjuvant chemotherapy response by ACT in breast cancer was observed 86%. Ueno NT *et al*., had shown that neoadjuvant chemotherapy with FACVP in locally advanced breast cancers, disease-free survival (DFS) at 15 years was found 44% in patients who had a complete response, 31% in those who had a partial response (PR) and 7% in those who had less than a partial response [9]. Comparing the treatment, response of primary tumor between the two arms, there was no significant difference in complete response, partial response and stable disease. This result was not statistically significant. In ACT group maximum are in age group of (31-40) years which was 15(42.9%) cases followed by (41-50) years, (51-60) years and (20-30) years, which is 11(31.4%) cases, 6(17.1%) cases and 3(8.6%) cases respectively. In FACVP group majority are in the age group of (31-40) years which was 16(45.7%) cases followed by (41-50) years, (51-60) years and (20-30) years which were 12(34.3%) cases, 2(5.7%) cases and 5(14.3) cases respectively. So more than 40% patient in both group were relatively in younger age. The mean age in ACT and FACVP groups were 42.45±8.99 and 40.97±8.13 years respectively. The difference was not statistically significant. Similar result was also reported by Banks and Can fell (2009) [10]. The distribution of study population according to education by groups was recorded in this study. In 35 patients in ACT group maximum are illiterate which was 15(42.9%) cases

followed by primary level, secondary level, higher secondary level and others which were 8(22.9%) cases, 7(20.0%) cases, 4(11.4%) cases and 1(2.9%) case respectively. In 35 patients in FACVP group majority are illiterate which is 22(62.9%) cases followed by primary level, secondary level which are 10(28.6%) cases, 3(8.6%) cases respectively. The distribution of risk factors by groups was reported in this study. Oral contraceptives are taken in highest number both in ACT group (51.4%) and FACVP group (60.0%). Similar result was reported by McPherson *et al*., [11] and mentioned that while women are taking oral contraceptives there was a small increase in the relative risk of developing breast cancer. There was no significantly increased risk of having breast cancer diagnosed ten or more years following cessation of the oral contraceptive agent. Women who begin to use before the age of 20 appear to have a higher relative risk than women who begin to use oral contraceptive at an older age [11]. Family history of breast cancer was found (2.9%) in ACT group and (5.7%) in FACVP group respectively. Similar result was reported by McPherson *et al*., (2000) [11] and mentioned that first-degree relative like mother, daughter, sister who has had breast cancer, or multiple relatives affected by breast or ovarian cancer especially before they turned age 50, higher risk of getting breast cancer is more. Past history of breast disease and nipple discharge is found in only ACT group which is 1(2.9%). Similar result also reported by Sainsbury *et al*., (2000) [12]. The distribution of side of lump by groups effectively. Left sided lump was found in 16(45.7%) cases and 19(54.3%) cases in ACT group and FACVP group respectively. Only 2(5.7%) cases are found in both sides. This difference was not statistically significant. The distribution of lump in axilla (lymph node) by groups is recorded. Before chemotherapy axillary lump was palpable in 34 (97.1%) and 34(97.1%) cases in ACT and FACVP group respectively. After chemotherapy axillary lymph node became non-palpable which were 15(44.1%) and 14 (41.2%) cases in FACVP and ACT group respectively. So, response rate of chemotherapy over axillary lump was slightly more in FACVP group. But still the difference was not significant. Ash Kari *et al*., (1976) [13] was reported a similar study and mentioned that experience with breast cancer presenting as an axillary mass in 42 patients had been reviewed according to initial clinical findings, treatment and survival. Medina-Franco and Urist (2002) [14] were also reported a similar result. The distribution of general examination by groups is recorded in this study. Appearance good is found more in ACT group than FACVP which were 21(60.0%) cases and 13(37.1%) cases respectively. Appearance ill looking was found more in FACVP group than ACT group which are 22(62.9%) cases and 14(40.0%) cases respectively. The difference is significant. Body build is good in 9(25.7%) cases and 5(14.3%) cases in ACT group than FACVP respectively. Body build is average in 21(60.0) cases and 17(48.6%) cases in ACT group than FACVP respectively. Body build is below average in 5(14.3%) cases and 17(48.6%) cases in ACT group than FACVP respectively. Anemia was found in 34 (97.1%) cases and 33(94.3%) cases in FACVP group than ACT groups respectively. Jaundice is present in 1 (2.9%) case in both ACT group than FACVP groups. Edema was present only in 1(2.9%) case in FACVP group. Dehydration is present in 14 (40.0%) cases and 19(54.3%) cases in ACT group than FACVP groups respectively. Palpable neck node is found in 2 (5.7%) and 3(8.6%) cases in ACT group than FACVP groups respectively. Bonadonna and Valagussa (1981) [15] were reported a similar result. The mean of investigations variables by follow up is recorded in this study. The mean hemoglobin concentration was 10.81±0.97 and 10.31±1.00 in the ACT group in before and after the treatment which is statistically significant. The mean hemoglobin concentration is 10.66±1.24 and 10.04±1.08 in the FACVP group in before and after the treatment which was statistically significant. The mean total count of WBC was 8390.54±2483.11 and 10020.00±16638.05 in ACT group in before and after the treatment respectively which was statistically not significant. The mean total count of WBC was 13952.86±22223.61 and 7722.86±1998.69 in FACVP group in before and after the treatment respectively which is not statistically significant. The mean ± SD of investigations variables by follow up was recorded in this study. The mean Platelet was 230634.86±77914.50 and 220257.1±74237.83 in ACT group in before and after the treatment respectively which is not statistically significant. The mean Platelet is 228657.14±44283.81 and 228485.71±40962.23 in the FACVP group in before and after the treatment which is not statistically significant. The mean ESR is 64.57±33.96 and 39.56±19.30 in ACT group in before and after the treatment respectively which was statistically significant. The mean ESR is 48.11±25.37 and 56.20±24.29 in FACVP group in before and after the treatment respectively which was statistically significant. The mean of investigations variables by follow up is recorded in this study. The mean SGPT is 26.26±6.14 and 40.43±50.22 in ACT group in before and after the treatment respectively which was not statistically significant. The mean SGPT was 29.23±6.66 and 30.88±8.00 in the FACVP group in before and after the treatment which was not statistically significant. The mean alkaline phosphates was158.62±37.00 and 193.54±112.66 in ACT group in before and after the treatment respectively which was not statistically significant. The mean alkaline phosphates were 165.01±22.83 and 170.84±21.09 in FACVP group in before and after the treatment respectively which is not statistically significant. The mean Bilirubin was 0.58±0.13 and 0.54±0.12 in ACT group in before and after the treatment respectively which was not statistically significant. The mean Bilirubin was 0.56±0.10 and 0.63±0.16 in FACVP

group in before and after the treatment respectively which was statistically significant. Similar result was shown by Kuerer *et al*., (1999) [16]. The patient and tumor characteristics associated with a complete pathologic response (pCR) in both the breast and axillary lymph node specimens and the outcome of patients found to have a complete pathological response (pCR) after neoadjuvant chemotherapy for locally advanced breast cancer (LABC) and concluded that neoadjuvant chemotherapy has the capacity to completely clear the breast tumor and involved axillary lymph nodes before surgery. Patients with locally advanced breast cancer who have a complete pathological response in the breast and axillary nodes have a significantly improved disease-free survival rate. In another study Schwartz *et al*., (1994) [17] reported a 10% pCR rate in the primary tumor after the administration of cyclophosphamide, methotrexate, 5-fluorouracil and anthracycline containing neoadjuvant chemotherapy to 156 LABC patients. In contrast, in another recently reported large series, Bonadonna *et al*., (1998) [18] administered several neoadjuvant drug regimens or mitoxantrone containing combinations; or doxorubicin alone) to 536 operable breast cancer patients and found a pathologic complete remission in the primary tumor in only 3% of patients. In a similar series of 212 patients reported by Powles *et al*., (1995) [19], a complete pathologic response in the primary tumor was found in 10% of the patients randomized to preoperative chemoendocrine therapy [20].

CONCLUSION

In conclusion, the findings of this study permit to conclude that neo-adjuvant chemotherapy is beneficial in treating the patients of locally advanced & metastatic breast cancer. For breast cancer to shrink a tumor a patient may receive neoadjuvant chemotherapy that is inoperable in its current state, so it can be surgically removed. It also reduces the chance of micro metastasis & there by improve the survival benefits. As adjuvant chemotherapy, Neoadjuvant chemotherapy is given in the same manner. To allow breast conservation, a woman whose tumor can be removed by mastectomy may instead receive neoadjuvant therapy to shrink the tumor enough. Our result indicates that, neoadjuvant chemotherapy with FACVP which is cheap, cost effective and equally responsive in patients with locally advanced & metastatic breast cancer patients in Bangladesh in comparison to ACT therapy. FAC protocol is standard therapy in breast cancer diseases. Addition of two non-myelo suppressive drug like vincristine and oral prednisolon is beneficial as an adjunct to FAC, thereby decrease in morbidity and mortality in comparison ACT therapy. The response was independent of age and grade of tumor.

LIMITATION

Small sample size was taken in this study. It was single center study with randomized sampling methods followed. The study and follow up period was short in comparable to other series. Receptor study of the breast cancer patients was not done.

RECOMMENDATION

A large scale study should be done to evaluate. Neo-adjuvant chemotherapy should be applied as the treatment. Additional randomized control trial with large sample size and longer time are necessary to support the result and prognoses that have been achieved with chemotherapy which bear low cost (FACVP) may be an option for treatment of breast cancer patients in Bangladesh. Further multi-center study with longer period for follow up should be needed to see the long term efficacy, safety and survival benefit of breast cancer patients.

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