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STUDY OF RESULTS, TOXICITIES AND COMPLIANCE OF NEO-ADJUVANT CHEMOTHERAPY (CAF/CMF) IN BREAST CANCER.

General Surgery

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ABSTRACT

20 patients of histologically proved and locally advanced breast cancer were evaluated for response to Neo-Adjuvant chemotherapy by clinical methods, Mammography and USG after 2nd and 4th cycle of chemotherapy and results were compared. It is seen that results i.e. response to CAF (Cyclophosphamide/Adriyamycin/5-Flurouracil) is excellent. Only in 1 patient having cardiological problem inplace of Adriyamycin Methotrexate used.

KEYWORDS

INTRODUCTION

Breast cancer is the commonest malignancy of females in the world and second most common cancer of females in India. (1)

Though majority of patients present with early breast cancer in western countries due to increased awareness and screening programmes, but most of the patients in our country still present with either locally advanced or metastatic breast cancer.

Twenty female patients of histologically proved breast cancer with T3 & T4 lesions, aged bellow 65 years were included in this study. Staging done by clinical examination, x-ray chest, skeletal survey, baseline mammogram & ultrasonography of breasts and abdomen.

Response to NACT were assessed clinically, U.S.G. & mammography after 2nd cycle of chemotherapy. In case of good response to NACT, reassessment again done after 4th cycle NACT, for planning of surgery i.e. breast conservation surgery or modified radical mastectomy.
It is seen that tolerance to this chemotherapy regimen is good and the toxicities, all most minor recorded in details.

MATERIAL AND METHODS

Twenty female patients of histologically proved breast cancer were included in this study. Informed consent was taken from all patients. Patients with large T2 (>4 cm), T3 and T4 lesion s were included in this study. Patients with age >65 years, small tumors (<4 cm) and those with metastatic disease were excluded.

Staging was done by clinical examination, X-ray chest, skeletal survey, a baseline Mammogram and Ultrasonography of breast & abdomen.

Routine work up included complete blood picture, liver function tests, renal function tests, ECG and Echocardiography.

Based on preoperative assessment, patients were categorized – a) Those who were suitable for breast conservation surgery (WLE or quadrantectomy + Axillary clearance). b) Those who were are not suitable for breast conservation.

All patients joining the trial were fully informed on the object of trial.
Chemotherapy regimens: CAF or CMF were used in following schedule:-

Cyclophosphamide 600 mg/m2 IV day 1, 8
Adriyamycin 30 mg/m2 IV day 1, 8
OR
Methotrexate 40 mg/m2 IV day 1, 8
5-fluroracil 600 mg/m2 IV day 1, 8

For patients with altered cardiac function, CMF regime was used. Instead of adriamycin, methotrexate was given 40 mg/m2 IV day 1 and 8.

All patients were advised to take light food on the day of chemotherapy and injection Ondensetron 8 mg IV was given before chemotherapy.

A peripheral blood count was performed before each course of chemotherapy and if TLC was found less than 4000/mm3, chemotherapy was postponed.

All patients were assessed clinically, mammographically and by USG after 2nd and 4th cycle of chemotherapy, to assess tumor response.

Clinical assessment of tumor response

Maximum diameter of the tumor was measured by calipers – Two greatest perpendicular diameter of the tumor was in the breast was taken and product of both was taken as overall clinical tumor.

Response was categorized as follows:

a. Complete Response : Total disappearance of primary tumor and lymphnodes.

b. Partial Response : Greater than 50% reduction of the product of two perpendicular diameters.

c. Stable Response : Reduction of tumor size < 50% or increase in tumor size < 25%.

d. Progressive : Increase in tumor size in > 25%
Mammographic Assessment

Bilateral mammograms were obtained during baseline staging and was repeated after 2nd and 4th cycle of chemotherapy for the affected breast.

Pre and post treatment mammograms were assessed by consultant radiologist.

The following criteria was assessed :

a. Mass : Size measured on mammogram using a scale in three perpendicular directions (two maximum dimensions considered). The shape and margins of the lesion and its density compared with the adjacent breast parenchyma.

b. Microcalcification : Distribution and extent.

c. Associated features : Architectural distortion, skin thickening, nipple retraction, additional masses and associated lymphadenopathy.

Response assessment by Mammography

a. Complete response : Complete resolution of mass at mammography with no residual abnormality

b. Partial mammographic response : suggested by the following features.

I. Mass resolved in mammography but microcalcification present.
II. Variable decrease in size and density of mass.
III. Decrease in size of a mass with no change in density.
IV. Size unchanged but density decreased.

c. Stable disease : - Findings unchanged from previous mammographic examination.

d. Progressive disease : Enlargement of mass or increase in the extent of abnormality.

Ultrasonographic Assessment

Ultrasonography was done both as a baseline (pre chemotherapy) and after 2nd and 4th cycles of chemotherapy to see the response. Baseline study included assessment of both breasts for tumor size, shape, margins and echotexture.

Response assessment by USG:

1. Complete Response : Complete disappearance of the mass with no residul abnormality

2. Partial Response : Tumor size reduction > 50%.

3. Stable Response : Reduction < 50% or increase in size < 25%.

4. Progressive : Tumor size increasing > 25%.

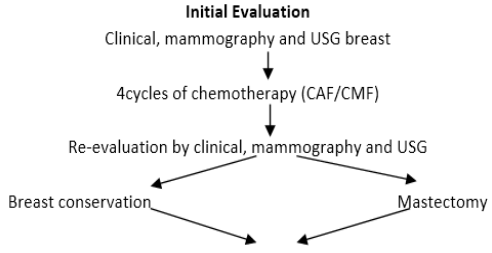
In addition bilateral axillae and the liver was olso evaluated on ultrasound for any abnormality and for staging.

Following completion of 4 cycles of chemotherapy patients were reassessed clinically, mammographically and by Ultrasonogram and suitability for breast conservation was assessed.

The actual surgical procedure performed was then recorded. A detailed histopathalogical evaluation was done and a formal pathological TNM (pTNM) staging was recorded.

Postoperatively completion chemotherapy and/or radio therapy was given where indicated. Patients were followed up regularly in breast cancer clinic and any evidence of locoregional or distant metastasis was recorded.

Flow diagram showing the treatment protocol : -



Comparision of response assessment by clinical methods, Mammography, USG by correlation of histopathological examination reports of the post operative specimens.

RESULT

Table showing Distribution of patients according to Age. Tumour size, Lymph node status

Age Grps(yrs)	No.	%
20-30	2	10
31-40	5	25
41-50	9	45
51-60	4	20
Tumor size (cm)		
5-6	11	55
6-7	3	15
7-8	2	10
8-9	4	20

20 female patients with breast cancer were included in this study, conducted in the department of surgery between 1999-2000. The demographic data of the patient is as follows:

Age: Mean age of the patient was 44.65 years with a range of 29-60 years. Age distribution and percentage of patients undergoing study is shown in table 1 as follows:

Table 1:

Age Group (years)	No. of patients	Percentage
20-30	2	(10%)
31-40	5	(25%)
41-50	9	(45%)
51-60	4	(20%)

Menopausal Status

10 Patients were premenopausal and 2 patients were perimenopausal and 8 patients were post menopausal of which 2 patients had undergone hysterectomy.

Tumor size (T Status)-

Tumor size of the patients is shown in table 2 as follows:

Table 2:

Tumor	No. of patients	Percentage
T2 (4-5 cm)	5	(25%)
T3	7	(35%)
T4a	8	(40%)

Details of tumor size are shown in table 3 as follows:

Table 3:

Tumor size in cm	No. of patients	Percentage
4-5	5	(25%)
5-6	6	(30%)
6-7	3	(15%)
7-8	2	(10%)
8-9	4	(20%)

Distribution of patients according to lymph node status is shown in Table 4 as follows:

Table 4:

Lymph node (N)	No. of patients	Percentage
Node negative	9	(425%)
Node positive	11	(55%)
Total	20	(100%)

Distribution according to Clinical staging (TNM) is shown in the Table 5 as follows:

Table 5:

Tumor	No. of patients	Percentage
IIA	4	(20%)
IIB	4	(30%)
IIIA	4	(10%)
IIIB	8	(40%)

Neoadjuvant Chemotherpy:

19 patients received CAF and one patient received CMF regimen. All patients received preoperative chemotherapy. 14 patients completed all 6 cycles. 5 patients took only one cycle of postoperative

Chemotherapy Tolerance:

19 patients tolerated the chemotherapy well, except minor toxicities. One patient developed severe low TLC, sore throat, nausea, vomiting etc for which she was hospitalized and treated. Toxicity due to chemotherapy is given in table 6.

Overall toxicity distribution and most common toxicities are shown in Table 6 as follows:

Table 6:

Overall toxicity	Post Op (n = 20)	Pre Op (n = 20)		
	No. of Patients	Percentage	No. of Patients	Percentage
None	9	45	9	45
Grade I	10	50	10	50
Grade II	0	0	0	0
Grade III	0	0	0	0
Grade IV	1	5	1	5

WBC Count Grade I (3.0-3.9)X103 Grade II (2.0-2.9)X103 Grade III (1.0-1.9)X103 Grade IV (<1.0)X103	6 2 1 1	30 10 5 5	2 1 1 0	10 5 5 0
INFECTION Severe Life threatening Death	0 0 0	0 0 0	0 0 0	0 0 0
SEPTIC EPICODE	0	0	0	0
NAUSEA Decreased dietary intake (Grade 2) No dietary intake (Grade 3)	6 0	30 0	4 0	20 0
VOMITING 6-10 episodes/d Parenteral support required	1 0	5 0	0 0	0 0
DIARRHOEA 7-9 times stool/day 10+ times /d, bloody stool or parenteral support required	1 0	5 0	0 0	0 0
STOMATITS Unable to eat Parental support required	6 0	30 0	4 0	20 0
ALOPACIA Mild Pronounced Complete	2 3 15	10 15 75	2 3 15	10 15 75
PHLEBILITIS/ THROMBOEMBOLISM Supf.	3	15	4	20

Post Chemotherapy Evaluation

Clinical Response

The overall response rate of the primary tumor to the neo-adjuvant chemotherapy was 95% (complete response 45%, partial response 50%). One patient had progression of disease and was offered surgery after two cycles. However, for some personal reasons she delayed the surgery and got operated only after four cycles.

Distribution of patients according to clinical response is shown in table 7 as follows:

Table 7:

Response	No. of Patients	Percentage
Complete response (CR)	9	45%
Partial response (PR)	10	50%
No response (NR)	0	0%
Progressive	1	5%
Total	20	100%

Post Chemotherapy down-staging shown in the table 8 as follows:

Stage	No. of patients			(%)
	Pre Chemotherapy		Post Chemotherapy	
No tumor (Clinically)			9	(45%)
I			5	(25%)
IIA	4	(20%)	4	(20%)
IIB	4	(20%)	2	(10%)
IIIA	4	(20%)	0	(00%)
IIIB	8	(40%)	0	(00%)

Mammographic Response

18 patients underwent Mammographic examination before neo-adjuvant, while 19 patients had mammogram done following chemotherapy. In one patient mammogram did not show any measurable lesion and thus pre and post chemotherapy mammogram could be compared in 17 patients. Overall mammographic response rate was 82.2%. Responses were complete in 2 (11.7%) patients and partial in 12 (70.5%) patients. No response / or progressive in 3 (17.6%) patients.

Distribution of patients according to mammographic response is shown in table 9 as follows:

Table 9:

Response	No. of Patients	Percentage
Complete response (CR)	5	25%
Partial response (PR)	12	60%
No response (NR) / Progressive	3	15%
Total	20	100%

Ultrasonographic response

17 patients underwent ultrasonographic examination of the breast before starting neo-adjuvant chemotherapy while 19 patients underwent Ultrasonography, post CT. The overall objective response of primary tumor to neo-adjuvant chemotherapy was above 88.1% (complete 5.8% and partial 82.3%).

Distribution of patients according to ultrasonographic response is shown in table 10 as follows:

Table 10:

Response	No. of Patients	Percentage
Complete response (CR)	1	5.8%
Partial response (PR)	14	82.3%
No response (NR) / Progressive	1	11.7%
Total	16	100%

Histopathological Evaluation

Complete histopathological response seen in five patients (25%) in whom there was no evidence of any microscopic disease in the resected breast or lymphnodes. All other 15 patients had evidence of invasive microscopic disease in the specimen. Histopathologic evaluation of those 11 patients who underwent MRM revealed that 6 patients in this group were potentially suitable for breast conservation due to either absence of any microscopic disease or presence of very small residual disease. Rest five were unsuitable for breast cionservation. The findings are summarized as below:

Histopathological evaluation of surgical specimen

- Pathological CR 5 (25%)
- Histopathological evaluation of mastectomy (11)
- Potentially suitable for breast conservation 6 (53%)
- Unsuitable for breast conservation 5 (45%)

DISCUSSION

Neo-adjuvant chemotherapy is being used increasingly in the treatment of patients with large operable and locally advanced breast cancer with the aim of reducing the size of the primary tumor and eliminating micro metastasis, in order to improve prognosis (2, 4, 5).

A wide variety of regimens have been used as neo-adjuvant chemotherapy. Most regimens incorporate doxorubicin (Adriyamycin). These regimens produce a complete pathological remission ranging from 3-18%. We used CAF in 19 patients while one patient received CMF. There are no randomized trials comparing CAF with CMF in the setting of neo-adjuvant chemotherapy. Two trials have suggested that response rates are lower with CMF (6, 7). In a previous trial reported from AIIMS NEW DELHI, significantly better response rates were seen with CAF regiment as compared to CMF (7). Therefore we prefer CAF in neo-adjuvant setting and use CMF only if there is any contraindication to use CAF. There is no apparent trend towards better response among various doxorubicin containing regimens (4).

Nineteen of our patients (95%) showed some degree of tumor reduction. Nine patients (45%) had complete clinical response, while 10 patients showed partial response (50%). Only one patient had progression of disease on clinical examination. These response rates are similar to those reported in literature using different regimens (8,9).

Singletary et al (8) used three cycles of vincristine, doxorubicin, cyclophosphamide and prednisone (VACP) at 21 day intervals and found 16% complete clinical response and 84% partial clinical response of which 23% became potential candidates for breast conservation surgery.

Scholl et al (9) used 4 cycles of CAF as neo-adjuvant chemotherapy and achieved objective rates of 65%. A complete clinical response rate 66% and overall response rate 98% was reported by Smith et al (10), using chemotherapy regimen requiring continuous infusion of drugs for 6 months. But in this study patient compliance was not good and complications were common.

In our study, the regimen used, resulted in excellent patient compliance and low incidence of minor toxicities, like vomiting, anorexia, superficial thromobophelbitis etc. Only one patient develope severe neutopenia for which she was hospitalized and treated. She subsequently received scheduled preoperative chemotherapy. All other patients completed scheduled chemotherapy.

Clinical response rates are believed to be important because this may correlate with patient survival (9) and also help in deciding the further surgical treatment. However it is found that response to chemotherapy is over estimated with clinical examination (11,12). As many as one third of patients thought to be in complete remission on clinical grounds, may have residual disease on pathological examination (13, 14). On the other hand persistence of residual abnormalities on physical examination or mammography does not always mean persistence of pathological disease (13).

In our study 9 patient had clinical CR but only 5 patient had pathological CR, 3 out of 9 patients who had clinical CR, pathologically they had complete response. On the other hand, 2 patients, those who had partial response clinically, were found in complete remission pathologically.

Therefore, in addition to clinical examination, patients in our study were also assessed by mammography and ultrasonography at the end of 2nd and 4th cycle chemotherapy.
Mark C. Segal et al reported excellent and moderate mammographic response in 82% cases. Cocconi's et al (6) reported a complete response rate of 8% with clinical examination, of 0% with mammography and of 14 % with pathologic examination.

Assessment of response to therapy by imaging modalities is important because this is crucial in choosing optimal surgical therapy and also because clinical examination often overestimates in tumor size (15, 16).

In our study, the response to neo-adjuvant chemotherapy was assessed by mammography in 17 cases and by ultrasonography in 16 cases. Mammography response was seen in 82% cases (15). Cocconi et al (6) reported a complete response rate of 8% with clinical examination, 0% with mammography. In one patient with clinically palpable lesion, mammogram did not show lesion due to the presence of dense glandular parenchyma.

When we compared clinical CR to clinical nodal status at presentation, it was found that four out of 11 lymphnode positive patients (37%) had clinical CR as compared to 5 out of 9 node negative patients (55%). This is consistent with findings of Fisher et al (5) who found that C-CR rates were nearly similar in patients with $\geq$5 cm tumors regardless of their nodal status at presentation. In contrast only 1 out of 9 clinically node negative patient (11%) showed pathological CR as compare to 4 out of 11 node positive patients (37%). This is also consistent with findings of Fisher et al (5) who found pCR to be higher in women with clinically positive nodes as compared to women with clinically negative nodes (30% vs 24%).

SUMMARY & CONCLUSIONS

20 patients of histologically proven large operable and locally advanced breast cancer were evaluated for response assessment by clinical methods, mammography and USG following down staging by neo-adjuvant chemotherapy after second cycle of chemotherapy and finally before operation.

19 patients received CAF and 1 patient received CMF regimen. Clinically, 9 (45%) patients had complete response, 10 (50%) patients had partial response and 1 (5%) had progressive disease.

19 patients received CAF and one patient received CMF regimen. All patients received preoperative chemotherapy. 14 patients completed all 6 cycles. 5 patients took only one cycle of postoperative

19 patients tolerated the chemotherapy well, except minor toxicities. One patient developed severe low TLC, sore throat, nausea, vomiting etc for which she was hospitalized and treated.

Thus we conclude that efficacy, tolerance and compliance to CAF/CMF regimen is satisfactory.

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