

# Role of Neoadjuvant Chemotherapy with Cyclophosphamide, Adriamycin, 5-Fluorouracil (Caf Regimen) in Down Staging in Breast Cancer.

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## ABSTRACT

**Background:** The aim of the study is to assess the tumor response to neoadjuvant chemotherapy with cyclophosphamide, adriamycin, 5-fluorouracil (CAF regimen) in terms of decrease in breast tumor size (partial or complete clinically). To assess clinically the axillary lymph node status after neoadjuvant chemotherapy (conversion from palpable to non-palpable). **Methods:** Thirty female patients of breast cancer were studied for down staging with two cycles of CAF regimen given at interval of 21 days. After 21 days of second cycle patient's staging noted for effects. **Results:** Thirty female patients of breast cancer were studied. Maximum no. of patients between 31-40 years, mean age 46 years and median age 45 years, youngest patients 18 years, oldest patients 70 years, 22 patients responded to chemotherapy, out of 22, 1 (3.3%) showed a complete clinical response, 21 (70%) partial clinical response. Pre-menopausal 9/13 (69.2%) and post menopausal 13/17 (76.4%) showed clinical response, statistically not significant difference (df=1,  $\chi^2=1.33$ ,  $p>0.05$ ). Change in tumor size  $40.09\pm 25.20$  sq. cm mean size to  $21.88\pm 27.43$  sq. cm after chemotherapy was highly significant change ( $t=6.242$ ,  $p<0.001$ ). Overall response to chemotherapy was 73.3%, in stage II-87.5%, stage IIIA-75% and stage IIIB-50%. The overall response to axillary lymph node was 56.6%, statistically highly significant ( $p<0.001$ ). Main side effects nausea and vomiting (60%) and hair loss, 43.3%, but none necessitated stoppage of chemotherapy. As a consequence to primary chemotherapy, conservation surgery (lumpectomy with axillary clearance) could be done in 43.3% of patients. **Conclusion:** CAF Preoperative chemotherapy regime is a satisfactory modality of treatment for stage II and III breast cancer with positive response rate of 73.3%. The down staging thus obtained permits breast conservation surgery in 43.3% of patients. The chemotherapy regime is well accepted by patients.

**Keywords:** CAF Primary /neo adjuvant chemotherapy; down staging; breast cancer.

## INTRODUCTION

The management of breast cancer ranges from loco/regional control with modified radical mastectomy to multipronged approach of breast conservation surgical techniques. Breast conservation is possible only if the tumor size is reduced. Neo adjuvant chemotherapy is being used frequently before surgery in large and locally advanced breast cancers aiming diminution of primary tumor size and knocking out putative micrometastasis to improve survival.

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## MATERIALS AND METHODS

The study was conducted from May, 2005 to Nov 2007 in the Department of General Surgery in conjunction with Department of Radiotherapy, Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar. Informed consent was taken from all the patients included in the study.

**Patient population:** Thirty female patients with breast carcinoma, stage II and stage III (TNM according to standard AJCC 1997 staging) in were studied. Two cycles of CAF or FAC regimen Swenerton<sup>[1]</sup> were administered preoperatively as follows: - Cyclophosphamide 500 mg/m<sup>2</sup> I.V. day 1. Adriamycin (Doxorubicin) 50 mg/m<sup>2</sup> I.V. day 1, 5-Fluorouracil 500 mg/m<sup>2</sup> I.V. day 1 and 8. The cycle repeated after 21 days.

**Inclusion Criteria:** a) T<sub>1</sub>/T<sub>2</sub>/T<sub>3</sub> with N<sub>0</sub>/N<sub>1</sub> and M<sub>0</sub>;

b) Any T with N<sub>2</sub>/N<sub>3</sub> and M<sub>0</sub>; c) T<sub>3</sub>/T<sub>4</sub> with any N and M<sub>0</sub>.

**Exclusion Criteria:** Patient unfit for chemotherapy; previous antitumor chemotherapy, inflammatory breast carcinoma, concurrent other malignancy, of distant metastases and cardiovascular impairment were excluded.

**Evaluation:** a) A detailed history and systemic examination was carried out. The size of the breast lump of the patient was measured with Vernier calipers or measuring tape. Evaluation of response was carried out in terms of change in the TNM staging (before and after neo adjuvant chemotherapy). Down staging was evaluated after 21 days from completion of second dose of chemotherapy. The response was assessed as complete response, partial response, no change or progressive disease by standard criteria as Haywards et al.<sup>[2,3]</sup>

## RESULTS

Maximum number of patients fell in the age groups of 31-40 years. The mean age of study population was 46 years and median age was 45 years. The youngest patient was 18 years female and the oldest patient was a 70 years female. Out of 30 patients, 22 patients responded to neo adjuvant chemotherapy (73.3%). Out of 22 patients, complete response was shown by 1 (3.3%) patient while the remaining 21 (70%) patients showed partial response. Patients in age group 11-20 years and 41-50 years had maximally responded to chemotherapy (i.e. 100%), compared to those in age group 61-70 years (i.e. 33.3%). Out of 13 premenopausal patients 9 (69.2%) had clinical response to chemotherapy. In post menopausal group, out of 17 patients, only 13 (76.4%) patients had clinical response to chemotherapy. Difference between response with neo adjuvant chemotherapy among premenopausal and postmenopausal was found to be statistically not significant (d f = 1;  $\chi^2 = 1.33$ ;  $p > 0.05$ )

Mean tumor size in present study before chemotherapy was  $40.09 \pm 25.20$  sq.cm (range: 6.82–147.00 sq.cm) and that after chemotherapy was  $21.88 \pm 27.43$  cm<sup>2</sup> (range: 0-127.40 cm<sup>2</sup>). Change in tumor size after chemotherapy was found to be statistically highly significant ( $t = 6.242$ ;  $p < 0.001$ ). Present study showed 87.50% response to chemotherapy in stage II tumor, 75% response in stage IIIA and 50% response in stage IIIB tumor. Overall response to chemotherapy was 73.3% in stage II and stage III patients. Statistically highly significant difference was observed in clinical response to stage II tumor compared to that of stage III tumor ( $p < 0.001$ ).

Before neo adjuvant chemotherapy, twenty three patients were having clinically palpable auxiliary lymph nodes. Out of which 20 patients were having

mobile lymph nodes (N<sub>1</sub>) and 3 patients were having fixed axillary lymph nodes (N<sub>2</sub>). After neo adjuvant chemotherapy, only ten patients were having mobile palpable lymph nodes (N<sub>1</sub>). So overall response to axillary lymph nodes was 56.6%. Change in lymph nodes status from clinically palpable to non-palpable was found to be statistically highly significant ( $p < 0.001$ ).

The main side effects observed were nausea and vomiting (60%) and hair loss (43.3%) in all patients but none necessitated discontinuation of chemotherapy. Subsequent to preoperative chemotherapy, conservative surgery (lumpectomy with axillary clearance and segmental mastectomy with axillary clearance) could be done in 43.3% of the patients. Following surgery, all patients were discharged after removal of stitches. None had post-operative complications after surgery and follow up was done for prognosis and disease free survival for 12 months.

## DISCUSSION

In our study, out of 30 patients 22 have responded to neo adjuvant chemotherapy (73.3%). Out of 22 patients, complete clinical response was shown by one patient (3.3%) while the remaining patients (70%) showed partial clinical response. Different studies have shown clinical response range from 70% to 85% and clinically complete response 6.6 to 27%<sup>[4-8]</sup>. Hence, clinical response in present study also fell in the same range, but complete clinical response is less than that of different studies. The reasons for lower result in clinical complete response may be: (A) Our study group was very small (i.e. 30 patients) compared to other studies. (B) We have given only two cycles of CAF regimen preoperatively compared to 2 to 5 cycles of chemotherapy in other studies.

**Table 1: Staging Before and After Chemotherapy.**

Sr. No.	Staging	No. of patients before chemotherapy	No. of patients after chemotherapy
1.	Stage 0		1
2.	Stage I		7
3.	Stage II a T <sub>0</sub> N <sub>1</sub> M <sub>0</sub> T <sub>1</sub> N <sub>1</sub> M <sub>0</sub> T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>	5	8
4.	Stage II b T <sub>2</sub> N <sub>1</sub> M <sub>0</sub> T <sub>3</sub> N <sub>0</sub> M <sub>0</sub>	1 2	3 1
5	Stage III a T <sub>0</sub> N <sub>2</sub> M <sub>0</sub> T <sub>1</sub> N <sub>2</sub> M <sub>0</sub> T <sub>2</sub> N <sub>2</sub> M <sub>0</sub> T <sub>3</sub> N <sub>1</sub> M <sub>0</sub> T <sub>3</sub> N <sub>2</sub> M <sub>0</sub>	- - - 13 3	- - - 2 -
6.	Stage III b T <sub>4</sub> anyNM <sub>0</sub>	6	8

Any T N <sub>3</sub> M <sub>0</sub>	-	-
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Present study showed that patients in age groups 11-20 years and 41-50 years had maximally responded to chemotherapy (100%) compared to those in age group 61-70 years (33.3%). But the correlation between age of patients and change in tumor size after neo adjuvant chemotherapy was found to be statistically not significant ( $r = -0.13859$ ;  $p > 0.05$ ). It showed that there exists a negative but not significant correlation between age and change in tumor size which implies that as the age increases, the change in tumor size with neo adjuvant chemotherapy decreases although not significantly. Different studies have also shown that age is no specific criterion for clinical response to chemotherapy.<sup>[9]</sup>

Mean tumor size in present study before chemotherapy was  $40.09 \pm 27.43$  sq.cm (range: 6.82 – 147.0 sq.cm) and that after chemotherapy was  $21.88 \pm 27.43$  sq.cm (range: 0-127.40 sq.cm). Change in tumor size after chemotherapy was found to be

statistically highly significant ( $t = 6.242$ ;  $p < 0.001$ ). Maximum clinical response to chemotherapy was found in tumor size 2.1-4.0 cm (100%) and minimum response to chemotherapy in tumor size 12.1 – 14.0 cm (0%). Also, as the size of tumor increases response to chemotherapy decreases, 2.1 – 4.0 cm (response = 100%), 4.1 – 6.0 cm (response 77.7%), 6.1-8.0 cm (response 73.33%), 8.1 – 10.0 cm (response 50%), 12.1-14.0 cm (no response). One study showed that the response to chemotherapy decreased as the tumor size increased (tumor size <5cm 48% response, tumor size 5-10 cm 20% response and tumor size >10cm 4% response)<sup>[12]</sup>. Similarly a study concluded that tumor size < or = 2cm responded maximally to chemotherapy ( $p < 0.001$ )<sup>[10]</sup>. Another study concluded that tumor size had marked prognostic significance following chemotherapy.<sup>[11]</sup> So prognostic significance of tumor size in present study correlates with other studies.

**Table 2: Comparison of Response with Neoadjuvant Chemotherapy According to Stage of Tumor.**

Stage comparison	Df	X <sup>2</sup>	p-value	Response
II/IIIA	1	5.161	<0.05	Significant
II/IIIB	1	32.751	<0.001	Highly significant
IIIA/IIIB	1	13.355	<0.001	Highly significant
II/IIIA+IIIB	1	10.849	<0.001	Highly significant

Present study showed 87.50% response to chemotherapy in stage II tumor, 75% response in stage IIIA and 50% response in stage IIIB. Overall response to chemotherapy was 73.3% in stage II and stage III breast cancer patients. Statistically highly significant difference was observed in clinical response of stage II tumor when compared to that of stage III tumor ( $p < 0.001$ ). Different studies indicated better response to chemotherapy for stage II tumor (82-87%) when compared to response for stage III tumor (46–60%).<sup>[12,13]</sup> So results of our study also correlate with other studies.

In present study, 23 patients were having clinically palpable axillary lymph nodes out of which 20 patients were having mobile lymph nodes (N<sub>1</sub>) and 3 patients were having fixed axillary lymph nodes (N<sub>2</sub>). After chemotherapy, only 10 patients were having mobile palpable lymph nodes (N<sub>1</sub>). So overall response to axillary lymph nodes was 56.6% and change in lymph node status from clinically palpable to non palpable was found to be statistically highly significant ( $p < 0.001$ ).

In one study, 170 patients of locally advanced breast cancer were treated with neoadjuvant chemotherapy and 63% patients had negative axillary lymph nodes after chemotherapy.<sup>[14]</sup> Similarly, a study showed that metastatic lymph nodes were found to be a sovereign predictor of tumor response as well as relapse.<sup>[15]</sup> Hence, clinical response to axillary lymph nodes after neoadjuvant chemotherapy in present study correlates with the result of other studies. The prognostic value is greatest in aggressive tumour

subtypes.<sup>[16]</sup> The pathological response to preoperative therapy exhibits a complex interaction between the regimen delivered, the pathological complete response improvement, and long-term outcome, is not well understood.<sup>[17]</sup>

**Side effects of chemotherapy regimen:** Patients had nausea and vomiting as most common side effects during chemotherapy (60% cases), was controlled by antiemetic and antacid drugs. Second most common side effect noted among patients was loss of hair (43.3%). All the 30 patients completed two cycles of neoadjuvant chemotherapy.

**Procedures undertaken after chemotherapy:** As a result of down staging of tumor with neoadjuvant chemotherapy, breast conservation surgery was possible in 13 patients (43.3%). Following surgery, all patients were discharged after removal of stitches. None had post-operative complications. All patients received 5 cycles of chemotherapy after surgery and follow up was done for prognosis and disease free survival for 12 months.

## CONCLUSION

Based upon this study, we conclude that preoperative chemotherapy is a satisfactory modality of treatment for stage II and stage III breast cancer with a positive response rate of 73.3%. The down staging thus obtained permits breast conservation

surgery in 43.3% patients. The chemotherapy regimen is well accepted by patients.

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