

Research Article

A study of the effect of neoadjuvant chemotherapy with FAC regime in locally advanced breast carcinoma

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ABSTRACT

Background: Cases of carcinoma breast with TNM stage 3 are considered as locally advanced breast cancer. This study was done to demonstrate the effect of neoadjuvant chemotherapy in cases of stage 3 technically inoperable breast cancers. As neoadjuvant chemotherapy is an already established form of treatment, its effect on 'complete clinical response and pathological response' were studied.

Methods: This prospective study was carried out in department of general surgery of Medical college, Thiruvananthapuram after obtaining approval from research ethical committee. Relevant data of chemotherapy was collected from department of Radiotherapy and Histopathological data was collected from department of Pathology. 25 cases of locally advanced breast carcinoma were studied. These patients were started on treatment with FAC regime and the response was assessed.

Results: In this study 20% of patients had complete clinical response at the completion of 3 cycles of chemotherapy with FAC regime. 48% had partial response. In 32% of patients, stasis was observed. None showed increase in tumor size during treatment.

Conclusion: The study demonstrated the effectiveness of neoadjuvant chemotherapy in downstaging the tumor enabling definitive surgery with less morbidity. It also showed a complete clinical and pathological response in a significant number of patients.

Keywords: LABC, FAC regime, Chemotherapy

INTRODUCTION

Breast cancer is the most common site specific cancer among women worldwide. It accounts for about 33% of all female cancers. Despite an increasing incidence, mortality from breast cancer has continued to fall, thought to be the result of both earlier detection via mammographic screening and improvements in therapy. Current treatment of breast cancer is guided by recent insights into breast cancer biology, an increasing ability to define disease biology and status in individual patients, and the availability of improved treatments.¹ In India it is the second most common cancer after cancer of uterine cervix. Life style and reproductive

patterns has got an important role. Locally advanced breast cancer refers to stage III disease which includes T3 tumours with N1, N2 or N3 disease; T4 tumours with any N classification; or any T classification with N2 or N3 regional lymph node involvement.² There should not be evidence of distant metastasis. LABC includes inflammatory breast carcinoma (T4d) also.

METHODS

This prospective study was done in a government medical college in Thiruvananthapuram. The study was to evaluate the clinical and pathological response of

neoadjuvant chemotherapy by FAC regime (Fluorouracil, Adriamycin and cyclophosphamide) on locally advanced breast carcinoma. 25 patients with large or technically inoperable tumours from the surgical department were selected and evaluated in the prechemo, post chemo and post mastectomy periods, and collecting relevant data from the chemotherapy and pathology departments also.

Patients with evidence of metastasis and patients who had received chemo therapeutic regimes other than FAC were excluded. The patients with stage IIIa and IIIb disease were started on 3 – 4 cycles of neoadjuvant chemotherapy. The diagnosis of breast cancer was made cytologically by FNAC in 24 patients and by tru cut biopsy in one patient. Staging investigations such as chest X rays and ultrasonogram abdomen were done prior to chemotherapy. All the 25 patients were started on FAC regime given on day first and repeated at 3 weeks for 3 – 4 cycles.

Assessment of response and clinical measurements were taken prior to treatment in greatest dimension and after 3 cycles of neoadjuvant chemotherapy. The response was studied according to the standard UICC criteria ie; union for international cancer control.

A partial response was a reduction of greater than 50% in the products of the two maximum perpendicular diameters. A complete clinical response was no detectable tumor clinically and stasis was less than 50% reduction in the product of maximum perpendicular diameters. The reduction in skin ulceration and fixity and the feasibility of simple mastectomy(SM) and axillary dissection (AD) without the need for skin grafting or other reconstructive measures was assessed.

Following neoadjuvant chemotherapy all patients were scheduled for simple mastectomy and axillary dissection and the specimen subjected to histopathological assessment. All patients were scheduled for post operative radiation therapy to chest wall and axilla and supraclavicular area. Further chemotherapy for 3 – 6 cycles was also scheduled.

RESULTS

Of the 25 patients, 5 patients had complete clinical response ie, clinically not detectable (20%). 12 patients had partial responses ie, >50% reduction in tumour size (48%). 8 patients had stasis ie, <50% reduction in tumour size (32%). None of the patients showed increase in tumour size during treatment.

Table 1: Type of clinical response to the chemotherapy regime.

Regime	Complete clinical response	Partial response	Stasis
FAC	20%	48%	32%

Histopathological Assessment

Of the 5 patients with complete clinical response 2 patients showed pathological complete response ie, no tumour was detectable in mastectomy specimen or lymph nodes (8% of the study group).

Table 2: Pathological complete response in mastectomy specimen.

Regime	Complete pathological response
FAC	2 patients (8%)

The microscopic appearances after neo adjuvant chemotherapy include necrosis with adjacent bizarre nuclei and multinucleation, masked fibrosis in breast tissue, plump fibroblast and foamy macrophages at the site of neoplasm due to reaction necrosis of the tumour.

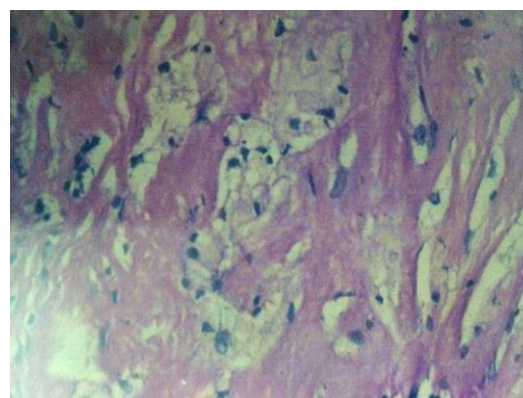


Figure 1: Microscopic picture from the mastectomy specimen after neoadjuvant chemotherapy, which shows marked fibrosis in breast tissue and plump fibroblast.

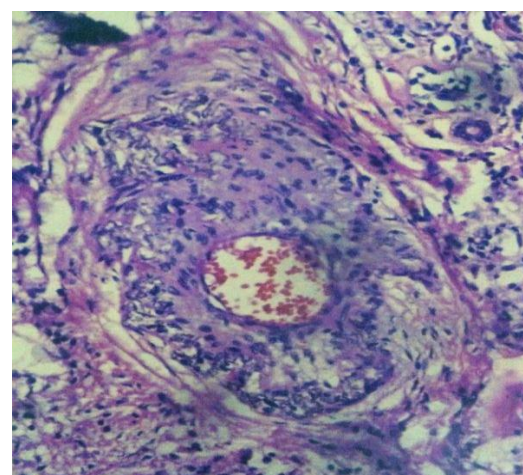


Figure 2: Microscopic picture from the mastectomy specimen, of a patient who underwent SM + AD after neoadjuvant chemotherapy, which shows blood vessel with thickened wall and proliferated endothelial cells.

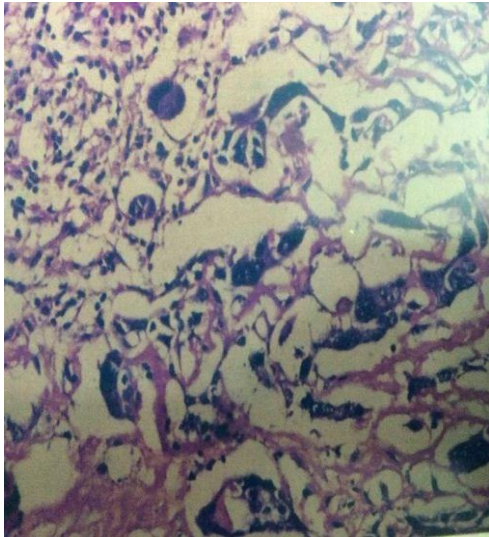


Figure 3: Microscopic picture of SM + AD after neoadjuvant chemotherapy showing bizarre nuclei and multinucleation.



Figure 4: Prechemotherapy picture showing skin involvement and ulceration.

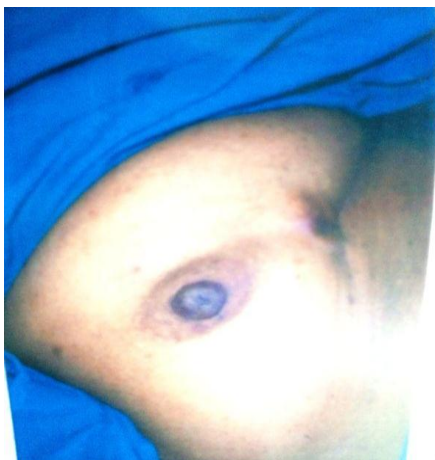


Figure 5: Post chemotherapy picture showing complete healing of the ulcer.

When student ‘t’ test was applied to pre and post chemotherapy tumor size values, the difference was statistically highly significant ($P < 0.001$).

Table 3: Pre and post chemotherapy tumour size and significance.

Regime	FAC
Pre chemo tumor size	10.73 cm
Post chemo tumor size	4.65 cm
Standard deviation	2.712
Standard error	0.531
P value	<0.001

DISCUSSION

Locally advanced breast cancer, LABC refers to tumour size more than 5 cm (T3) or tumor fixed to chest wall or presence of skin ulceration, satellite nodule or peau d orange or regional lymph nodes; but without evidence of distant metastasis (M0) and includes inflammatory breast carcinoma also.

Induction with neoadjuvant chemotherapy was tried to convert unresectable tumours to resectable ones. This also formulated an opportunity to have an increase of tumor sensitivity to a particular set of drugs. Reports from MD Anderson Cancer centre and National Institute Milan etc confirmed the superior results from neoadjuvant chemotherapy compared to initial radiotherapy alone in LABC. In Milan trial, the best results were achieved when surgery was interposed between chemotherapy courses, with 82% locoregional control and 25% 5 year disease free survival.³

MD Anderson group reported the results for non inflammatory inoperable breast cancer using chemotherapy FAC regime as the first treatment modality. They had an objective response rate of chemotherapy of about 82% (15% complete response). With selective use of surgery, local control was excellent (79% at 5 years) and overall with better understanding of the disease and team work amongst surgical, medical and radiation oncologists the treatment results have improved with the accepted 5 year survival rate over 60%. Survival rate at 5 years was 55%.

Neo adjuvant chemo therapy allows for immediate objective assessment of response. This response may be an important prognostication of the ultimate outcome and long term survival in patients with LABC. The neoadjuvant therapy allows for monitoring of treatment response and discontinuation of inactive therapy in the event of disease progression, thus saving the patient from exposure to potentially toxic therapy.⁴

The reduction in size of the tumour and it becoming more mobile and less fixed to skin obviates the need for skin grafting or complex reconstruction. It may also avoid the need for surgery in a previously irradiated field. Chemotherapy also decreases the intensity and morbidity of irradiation to treat the breast or chest wall. Disease progression during therapy are more likely to be larger tumours, have nodal metastasis, and have lymphovascular invasion on pathological evaluation.⁵ In our study, none of the patients showed disease progression during therapy.

Usually 3 cycles of neoadjuvant chemotherapy is generally accepted as standard before surgical therapy. Evidence from many series indicated that patients with rapidly responding cancers and those who achieve a complete remission have a better outcome than patients who do not have a good response to neoadjuvant chemo therapy. Neoadjuvant therapy has been found to lead to better control of systemic residual disease in animal model.^{6,7}

With better understanding of the disease and team work amongst surgical, medical and radiation oncologists the treatment results have improved with the accepted 5 year survival rate over 60%. Combination of surgical and chemo radio therapy yielded superior loco regional control.

CONCLUSIONS

The study demonstrated the effectiveness of neoadjuvant chemotherapy in down staging the tumour and enabling definitive surgery to be done with less morbidity. Moreover it helps to assess the response to chemotherapy and to change the chemotherapeutic regime if necessary. In our study, 20% of patients showed complete clinical response and 8% showed complete pathological response in mastectomy specimen.

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Ethical approval: The study was approved by the institutional ethics committee

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