A PROSPECTIVE STUDY ON ROLE OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

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ABSTRACT

A prospective study on role of neoadjuvant chemotherapy in locally advanced breast cancer is a prospective study which was conducted at Yenepoya Medical College, Mangalore during the period August 2010 to January 2013 to evaluate the response of neoadjuvant chemotherapy in locally advanced technically inoperable breast carcinoma. Study was aimed to evaluate the immediate response of locally advanced technically inoperable breast cancer to neoadjuvant chemotherapy. The response to CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and the overall response, to assess the reduction in the tumour size and the feasibility of mastectomy after neoadjuvant chemotherapy, to study the number of cases with clinical complete response, and to assess its pathological completeness, and to study the pathological response of breast cancer to neoadjuvant chemotherapy. In this prospective study, thirty–two patients with locally advanced breast cancer were followed up before and after neoadjuvant chemotherapy. Of the twenty seven patients on AC regime, five patients had clinical complete response (18.51%), 13 patients had partial response (48.15%) and nine patients had stasis (33.33 %). Thus, 10 patients (71.3%) had >50% reduction in the tumour size. Of the five patients on CMF regime, one had partial response (>50% reduction in the tumour size) and 4 patients had stasis (<50% reduction in the tumour size) and none had clinical complete response (CR). None of the patients in the CMF and AC regime showed increase in tumour size during treatment.

KEYWORDS

Locally Advanced Breast cancer, Neoadjuvant Chemotherapy, CMF Regime.

MeSH TERMS

Locally Advanced Breast Cancer, Neoadjuvant Chemotherapy.

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INTRODUCTION: Breast is the symbol of femininity and womanhood. Brest cancer is the most common and dreaded malignancy in women making it the second leading cause of cancer related deaths.[1] The incidence of breast cancer is found to be increasing. In developing countries like India, women seek proper medical attention in late stage only. In India according to ICMR registries of cancer in women, breast cancer is the commonest cancer in Delhi and Mumbai followed by cancer cervix. Ignorance, illiteracy, fear and poverty may be the reason for this. Screening programs and informative approaches should be rendered at the grass root level so that they may seek medical help in the very early stages of disease. Neoadjuvant chemotherapy, as a newer modality of treatment evolved during last 30 years, practiced all over the world for downstaging the technically inoperable locally advanced breast cancer prior to surgery.[2] This prospective study was conducted at Yenepoya Medical College, Mangalore during the period August 2010 to January 2013 to evaluate the response of neoadjuvant chemotherapy in locally advanced technically inoperable breast carcinoma.

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AIMS AND OBJECTIVES:

1. To evaluate the immediate response of locally advanced technically inoperable breast cancer to neoadjuvant chemotherapy. The response to CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil) and the overall response.
2. To assess the reduction in the tumour size and the feasibility of mastectomy after neoadjuvant chemotherapy.
3. To study the number of cases with clinical complete response and to assess its pathological completeness.
4. To study the pathological response of breast cancer to neoadjuvant chemotherapy.

MATERIALS AND METHODS:

Design: The study design was a prospective study.

Setting: The study was conducted in the Department of General Surgery and Department of General Surgery, Yenepoya Medical College Hospital, Mangalore during the period from August 2010 to January 2013.

MATERIALS AND METHODS: A prospective study to evaluate the response of neoadjuvant chemotherapy in patients with Stage III technically inoperable breast cancer was started in August 2010. 32 cases with large or technically inoperable locally advanced breast cancer were studied. These patients with stage IIIa & IIIb disease were

started on treatment. These cases were discussed with the radiotherapist and were started on neoadjuvant chemotherapy.

The diagnosis of breast cancer was histopathologically confirmed by FNAC and in one case biopsy was done. Staging investigations such as chest x-rays and ultrasonogram abdomen were done in all patients to exclude pulmonary or liver metastasis. Routine haemogram and ECG were done prior to chemotherapy.

Treatment Protocol: Of the thirty-two patients, twenty-seven were put on AC regime and five on CMF regime.

CMF Regime:

- Cyclophosphamide – 600 mg/m^2
- Methotrexate – 40 mg/m^2
- 5-fluorouracil – 500 mg/m^2
- Given on day one and eight- Repeated every four weeks for three to four cycles.

AC Regime:

- Adriamycin – 60 mg/m^2
- Cyclophosphamide – 600 mg/m^2
- Given on day first and repeated at 3-weeks for 3-4 cycles.

Assessment of Response: Clinical measurements using measuring tape were taken prior to treatment and after completion of neoadjuvant chemotherapy. The response was defined according to the standard UICC criteria. Partial response was a reduction of greater than 50% in the products of the two maximum perpendicular diameters, a complete response was no detectable tumour and stasis was less than 50% reduction or less than 25% increase in the product of the maximum perpendicular diameters. (Miller AB 1981). The regression of the size and number of the lymph nodes were also assessed and whether fixed lymph nodes had become mobile. The reduction in the skin ulceration and fixity and the feasibility of simple mastectomy and axillary dissection without the need for skin grafting or other reconstructive measures was assessed. The preliminary assessment was done after two cycles of chemotherapy and if needed the chemotherapy was continued for further 2-3 cycles.

Surgical Treatment: Following neoadjuvant chemotherapy, all patients were scheduled for simple mastectomy and axillary dissection and the specimen subjected to histopathological assessment. The pathological assessment of the residual tumour was also studied.

Post-operative Adjuvant Treatment: All patients were scheduled for postoperative radiation therapy to chest wall and axilla and supraclavicular area. Further chemotherapy for 3-6 cycles were also scheduled.

STATISTICS: Statistical methods applied were descriptive, Crosstabs, Chi-square and Independent-samples T test. SPSS for windows version-16 2007 was employed for statistical analysis.

OBSERVATIONS: In this prospective study, thirty two patients with locally advanced breast cancer were followed up before and after neoadjuvant chemotherapy (Fig.1, Fig-2 and Fig-3).

Response Rates: Of the twenty seven patients on AC regime, five patients had clinical complete response (18.51%), 13 patients had partial response (48.15%) and nine patients had stasis (33.33 %). Thus, 10 patients (71.3%) had >50% reduction in the tumour size. Of the five patients on CMF regime, one had partial response (>50% reduction in the tumour size) and 4 patients had stasis (<50% reduction in the tumour size) and none had clinical complete response (CR). None of the patients in the CMF and AC regime showed increase in tumour size during treatment (Table.1).

Overall out of the 32 tumours, 5(15.62%) had clinical complete response (CR) and 14 (43.75%) had partial response i.e. 19 tumours (59.32%) had objective clinical response. 13 (40.63%) had stasis.

Histopathological Assessment: All patients underwent simple mastectomy and axillary dissection and the specimens subjected to histopathological examination.

Complete Response: Of the five patients with clinical CR, all of them were AC regime. Two patients on AC regime were with pathological complete response (6.26%), i.e. no tumour detected in the mastectomy specimen or lymph nodes (Table 2).

The microscopic appearances after neoadjuvant chemotherapy include necrosis with adjacent inflammation, bizarre nuclei and multinucleation, marked fibrosis in breast tissue, plump fibroblast foamy macrophages at the site of neoplasm due to reaction to necrosis of tumour and blood vessel with thickened wall and proliferated endothelial cell.

When student 't' test was applied to the pre- and post-chemotherapy tumour size values in the CMF regime, the reduction was highly significant ($p < 0.01$). In the AC regime, the difference was statistically very highly significant ($p < .001$) (Table 3).

Toxicities: All patients experienced nausea and vomiting of various degrees for few days following chemotherapy. Almost all developed alopecia of varying degrees. Since Adriamycin is a cardiotoxic drug, patients were started on it only after talking ECG and cardiology consultation to rule out any pre-existing cardiac problem. Echo test was done prior to and after treatment. Patients with history of cardiac disease were not started on Adriamycin. No major cardiac toxicity found during the treatment periods. One patient developed congestive cardiac failure 8 months after completion of treatment and was promptly treated.

Psychological Acceptance: Regression of the tumour size as well as response rate of other patients evoked a psychological well-being for the patients who were very anxious and worried.

DISCUSSION: Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer: Locally Advanced breast cancer (LABC) generally refers to stage IIIa and IIIb.[3] The disease involes tumour size more than 5 cm (T3) or tumour fixed to chest wall/skin ulceration, satellite nodule or peau d' orange or regional lymph nodes but without evidence of distant metastasis (M0) and includes inflammatory breast carcinoma (T4) also.[3] The patients in this group have large volume of locoregional disease and high incidence of micrometastasis.

Fortunately with better understanding of disease and team work amongst surgical, medical and radiation oncologists, the results have improved remarkably with the accepted 5 yr. survival rate over 60%.[2] Till 1940, the 5 yr. survival rate in LABC was around 15%.[3] In operable cases, surgery was performed and the rest were subjected to radiotherapy. Combination of surgery and radiotherapy yielded superior locoregional control.[2] However, distant failure was still a major problem. Addition of single agent chemotherapy after surgery and radiotherapy reported to offer superior local control and survival.[4]

Induction with neoadjuvant chemotherapy was tried to convert resectable tumours to resectable ones.[5] This also formulated an opportunity to have an increase of tumour sensitivity to a particular set of drugs. In a prospective study at Guy's Hospital, patients were assigned either chemotherapy followed by radiotherapy or radiotherapy followed by chemotherapy as initial treatment for LABC and then subjected to maintenance chemotherapy, survival for both groups were similar. Hence, when this was compared with those who had radiotherapy alone, there was a definite survival advantage. Reports from MD Anderson Cancer Centre and National Cancer Institute, Milan, etc confirmed the superior results from neoadjuvant chemotherapy in LABC.[6]

M.D Anderson group (Hortobagyi GN et al) reported the results for non-inflammatory in operable breast cancer using chemotherapy FAC (Flurouracil, Adriamycin, Cyclophosphamide) as the first treatment modality. They had an objective response rate of chemotherapy of 82% (15% CR). With selective use of surgery local control was excellent (79% at 5 yrs.) and the overall survival rate at 5 yrs. was 55%.

Our study has shown that out of 32 patients, 15.62% had complete clinical response CR, 43.75% had partial response and 40.63% had stasis. We had pathological complete response in AC regime only i.e 7.46%. At National Cancer Institute, Milan (De lena et al 1978) combination chemotherapy given before local therapy achieved a 70% objective response rates (15% complete response CR) in 154 cycles of AV (Adriyamycin, vincristine) and reported 4 yrs. survival in the range of 50%.

In contrast to the standardised use of adjuvant chemotherapy to treat occult disease that may be or may not be present, primary chemotherapy allows for immediate objective assessment of response.[6] This may be an important prognostication of the ultimate outcome of the patients. Lack of response may indicate need to alter therapy. Neoadjuvant chemotherapy also can be used to test new drugs and regimes more rapidly than is possible for standard adjuvant strategies.

Neoadjuvant chemotherapy allows for important detailed studies of the relationship of different pathogenic and more molecular markers of responsiveness, which can advance our understanding of cancer biology and chemoresistance. Neoadjuvant chemotherapy makes unresectable to resectable and may reduce the scope and difficulty of surgery.[6] Its use will make it less likely skin grafts or complex reconstruction will be required and it may also avoid the need for surgery in a previously irradiated field. Chemotherapy also decreases the intensity and morbidity of irradiation needed to treat the breast or chest wall.[7]

A variety of neoadjuvant chemotherapy regimes and schedules have been evaluated. Some authors claim that the most effective regimes as guided by objective response criteria contain doxorubicin while others emphasise that there is no superiority for doxorubicin containing regimes.[6] Most clinical trials reported response rates of 50% to 90%. Clinical complete response (CR) generally occurs in less than 20% of patients and even fewer patients have no dectectable tumour in the surgical specimen (pathological complete respones) Hortobagyi GN 1997.

Usually three cycles of neoadjuvant chemotherapy is generally accepted as standard before surgical therapy. Since 1975, the National Cancer Institute has given women with locally advanced breast cancer neoadjuvant chemotherapy.[2]

Assessment of Response: Regarding the assessment of response, we have assessed the response by clinical messurement. It has limitations as clinical CR patients don't have a pathological CR in some cases. It helps to assess the gross reduction in size and the feasibility of surgery without the need for skin grafting and other reconstructive procedures. In our study in which all patients were subjected to simple mastectomy and axillary dissection, the subtle differences do not alter the treatment protocol. Other modes of assessment such as ultrasound and mammography have also been shown to have limitations. Investigations have shown mammography to be inaccurate in the measurements of residual disease for patients with neoadjuvant chemotherapy induced fibrosis (Cocconi G et al, 1984). According to Cocconi. G, up to one third of patients found to be histologically free of disease have residual abnormality by palpation or imaging. Newer modality such as MRI is proving to be useful in assessing response according to Abraham et al (1996). But it is too expensive investigative modality to assess response on our setting.

The significant reduction in size make these tumours more amenable to treatment. The reduction in size of the tumour, its area of skin fixity or chest wall fixity makes the tumors operable. All patients were subjected to simple mastectomy and axillary dissection. Earlier surgery in such patients was found to be too complex requiring skin grafting and extensive excision, thus increasing the morbidity. Many were even considered to be inoperable. Radiation therapy to such locally advanced tumour carried very high morbidity with only a palliative role. After the downstaging following neoadjuvant chemotherapy surgery can be done as in

patients with less advanced tumours, thus reducing the morbidity of the patient and the work load of the surgeon. The reduction in size of the tumour and it becoming more mobile and less fixed to skin obviates the need for skin grafting and complex reconstruction.

Many have questioned the need for mastectomy in those who have clinical complete response. The trialby Calais et al (1994) omitted surgery for patients with clinical and mammographic complete tumour regression following neoadjuvant chemotherapy treating them with radiotherapy alone.[4] Previous studies have shown local recurrence rates to be high in patients treated with radiotherapy alone. According to Pierce. L.J, (1992) neoadjuvant chemotherapy followed by radiation alone for patients with LABC has results in high locoregional failure rates with the acceptance of breast conservation therapy (BCT).[8] In the western world, early breast cancer investigators have advocated breast conservation in those patients who have significant reduction in the size of the tumour satisfying the criteria for breast conservation[9], "The Jefferson Medical College Philadelphia" subjected patients with locally advanced breast cancer to neoadjuvant chemotherapy and 55 of the 189 patients who have good response underwent BCT. The 5 yr. survival rate was higher in those who underwent BCT than those who underwent mastectomy (Schwartz et al 1994). This reflects the fact that the response of the primary is a good indicator of the response of the micrometastases to chemotherapy.[7] Similarly in an attempt to use BCT selectively for patients with locally advanced breast cancer, patients at the "University of Michigan" were assessed by surgical biopsy after intensive neoadjuvant chemotherapy. Only those with an apparent complete pathological response (28%) were treated by BCT, including breast and nodal irradiation. The other 72% were treated with modified radical mastectomy followed by chest and nodal irradiations. Overall survival was 54% at 5 years and locoregional control at 5 years was 72% (Merajver SD et al 1997). Newer agents like transtuzumab (Herceptin) 2 mg/kg IV 30 minutes weekly for six courses were increasingly used in higher centres with adequate response.

Thus, breast conservation therapy for patients with LABC with partial or complete response to neoadjuvant chemotherapy is still under investigation. In the treatment of a group of patients once found to be incurable even after radical mastectomy this is a great leap. There have been many attempts to predict the response of the tumour to adjuvant chemotherapy. Menopausal status, age, ER/PR status, etc. have been found to have no role in the prediction of response. Studies show that the tumour factors and not the patient factors determine the response to chemotherapy have been reported. The use of new biomarkers such as P53, bcl-2, angiogenesis, C-erb B-2 oncogene expression is being evaluated (Leek RD et al 1994 Krajeweski S et al, 1997, Gasparine G 1995).

Response of locally advanced breast cancer to neoadjuvant chemotherapy is found to be a prognostic factor in longterm survival in these patients. 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 chemotherapy (Feldman et al 1986). As patients with early stage breast cancers nodal status is an important prognostic variable with longterm outcome directly related to the number of involved nodes at surgery following neoadjuvant chemotherapy (Attria- Sobal et al 1993).[10] This seems to be case even though the number of positive nodes is reduced by preoperative treatment. Palpable axillary nodes usually respond in parallel with the response of the breast lump. Thus, according to this, patients in this study who had a good response to neoadjuvant chemotherapy have a better chance of longterm survival than those who do not have a good response. This may be due to the fact that the response of micrometastasis is similar to that of the primary.[11]

Before the advent of neoadjuvant chemotherapy, the longterm survival of patients with locally advanced breast cancer was bleak. The reports of single modality therapy (radiotherapy or surgery) in LABC uniformly described poor patient outcome (Rubens et al 1977). The 5-year survival of patients treated with surgery alone, radiotherapy alone or combination of surgery and radiotherapy are 36%, 29%, and 33% respectively. These poor results are accounted for by the inevitable development of distant metastasis disease even following optical local therapy (Hortobagyi 1996, Hortobagyi et al 1997, Gradishar W J 1996). With new adjuvant chemotherapy, the 5-year survival is reported to be around 55% (Hortobagyi et al 1983, Gardin et al 1995, Pisanky et al 1996). In this study, only the clinical and pathological response to neoadjuvant chemotherapy has been investigated. Further followup of the same group of patients for 3 to 5 years will demonstrate its effect on term survival.

SUMMARY AND CONCLUSIONS:

Summary: The patient with locally advanced breast cancer which was condemned as inoperable and incurable till recently, neoadjuvant chemotherapy is a beacon of hope. For tumours with wide area of skin fixity and ulceration, primary surgery is an unrealistic option. For large tumour, primary surgery will require skin grafting or reconstructive procedure such as flap cover. Patients who are to undergo radiation therapy and chemotherapy after the mastectomy, such procedure will add to the morbidity and delay treatment. The significant downstaging of the tumour by neoadjuvant chemotherapy makes it operable and lessen the morbidity of surgery. It enables definitive surgery to be done without the need for skingrafting or other reconstructive procedures. Axillary dissection also becomes easier after neoadjuvant chemotherapy.

Neoadjuvant chemotherapy also acts on the micrometastasis, thus improving the longterm survival. Researchers claim that removal of primary tumour triggers rapid growth of micrometastasis due to removal of inhibiting factors. Neoadjuvant chemotherapy prevents this spirt of growth of micrometastasis.

In our study, all tumours had significant reduction in size and none of them progressed during the treatment. Thus, neoadjuvant chemotherapy has proved useful in downstaging the tumour enabling definitive surgery to be done with less morbidity. Since we had 5 cases of residual neoplasm as margin positive, we hope newer drugs may be used in future. There are further trials going on in this field of neoadjuvant chemotherapy regarding newer chemotherapy regimes such as Taxane, Vinorelbine,

gemcitabine, high dose chemotherapy with stem cell rescue and tumour marker as predictors of response to chemotherapy.

Treatment of breast cancer is a field that continues to provoke a lot of debate.The large volumes of research in this field had added only to the controversies. It has also seen the paradigm shift of treatment philosophy from radical mastectomy to breast conservation therapy, but in the treatment of patients with locally advanced breast cancer neoadjuvant chemotherapy will continue to play a role.

CONCLUSION: This study demonstrated the effectiveness of neoadjuvant chemotherapy in downstaging the tumour and enabling definitive surgery to be done with less morbidity. Further studies are required to prove its influence on longterm survival.

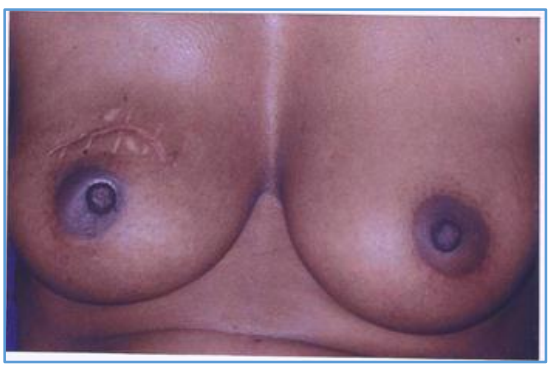

Fig. 1: Showing Locally Advanced Breast Cancer with Lump Excision Five Months Back

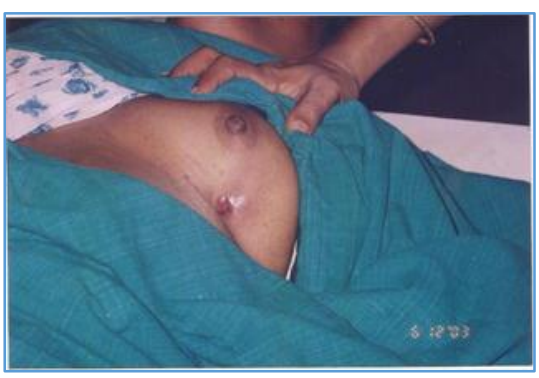

Fig. 2: Pre-chemotherapy Picture showing Skin Involvement and Ulceration

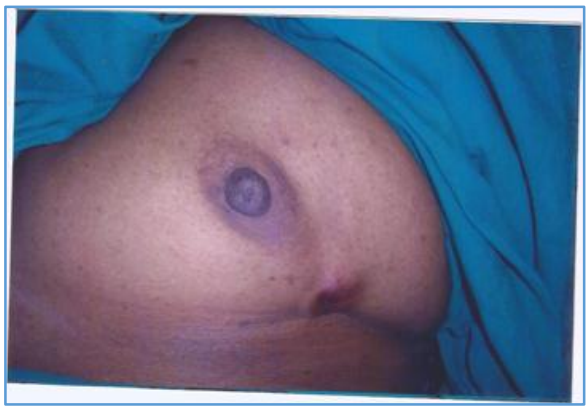

Fig. 3: Post-chemotherapy Picture Showing Complete Healing of the Ulcer

	Clinical CR (No Clinically Detectable)	**Partial Response (>50% Reduction In Tumour Size)**	**Stasis (<50% Reduction In Tumour Size)**
CMF(5)		1 (20%)	4 (80%)
AC (27)	5 (18.51%)	13 (48.15%)	9 (33.33%)
Total (32)	**5 (15.62%)**	**14 (43.75%)**	**13 (40.63%)**

Table 1: Showing the Response Rate in Neoadjuvant Chemotherapy

	Pathological CR
CMF (5)	0
AC (27)	2 (7.46%)
Total (32)	2 (60.25%)

Table 2: Showing Pathological Complete Response

	Pre chemo	**Post chemo**	**Std. Deviation**	**Std.Error**	**'T'**	**Significance**
CMF	11.65	7.00	2.793	1.249	3.68	P < 0.05
AC	10.73	4.65	2.712	0.531	11.4	P < 0.001

Table 3: Showing the pre- and Post-chemotherapy Tumour Size and Significance

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