International Journal of Research in Medical Sciences
Anand AS. Int J Res Med Sci. 2015 Dec;3(12):3474-3481
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20151241

Research Article

Study on the role of primary systemic chemotherapy with anthracycline combination schedule in locally advanced breast cancer: long term follow up data

Aravindh S. Anand*

Department of Radiotherapy and Oncology, Government Medical College, Thiruvananthapuram, Kerala, India

Received: 03 November 2015
Accepted: 19 November 2015

***Correspondence:**
Dr. Aravindh S. Anand,
E-mail: anandrt2006@yahoo.com

ABSTRACT

Background: Locally advanced breast cancer (LABC) refers to a heterogeneous group of locally advanced non metastatic group of breast cancer. Primary systemic chemotherapy (PST) which forms the prime modality in LABC management has several advantages. The objective of the study was to assess the response and survival of locally advanced breast cancer patients receiving PST with Anthracycline based combination chemotherapy in Indian setting.
Methods: 75 LABC patients who were treated with PST were observed and finally analyzed for survival. Chemotherapy schedules were FAC (5-Fluorouracil 500 mg/m2, Doxorubicin 50 mg/m2 and Cyclophosphamide 500 mg/m2) and FEC (5-Fluorouracil 500 mg/m2, Epirubicin 100 mg/m2 and Cyclophosphamide 500 mg/m2).Clinical complete response (cCR), partial response (PR), stable disease (SD) and pathological complete response (pCR) were assessed. 5 year overall survival (O.S) & disease free survival (DFS) were analyzed using Kaplan Meier survival analysis.
Results: 94% became operable after PST and 6% remained inoperable. MRM with axillary clearance was achieved in 70.4% while simple mastectomy with axillary dissection in 22.5%. Microscopic surgical clearance achieved in 85.9%. Objective clinical tumour response rate was 78.9% with cCR of 11.3%, PR of 67.6% & pCR of 7.5%. Five year O.S and DFS were 67.92% and 62.21% respectively.
Conclusions: Anthracycline based chemotherapy is an excellent schedule in neoadjuvant setting in LABC in down staging disease. But to further improve the O.S, DFS and pCR addition of agents like Taxanes and their sequencing must be explored. RCTs addressing these issues are warranted especially in countries like India.

Keywords: Locally advanced breast cancer, Primary systemic chemotherapy, Tumour response, Survival

INTRODUCTION

Locally advanced breast cancer (LABC) refers to a heterogeneous group of locally advanced non metastatic group of breast cancer. It includes clinically advanced primary tumour (T4 disease including inflammatory carcinomas) and advanced nodal disease (N2 & N3 disease). Clinical stage 111A, 111B & 111C of AJCC staging system for Breast cancer represents the clinical spectrum of LABC.[1]

The paradigm shift in the understanding of tumour biology has brought out several changes in management of breast cancer. Optimal management of LABC is complex. Primary Systemic chemotherapy (PST) otherwise called neoadjuvant chemotherapy (NACT) followed by local treatment in the form of surgery & radiation treatment and thereafter adjuvant systemic chemotherapy has become the standard of care for LABC.

Primary systemic chemotherapy which forms the prime modality in LABC management has several advantages.

It helps in reduction of tumour volume thereby down staging the disease. It increases the rate of radical surgery and even makes breast conservation surgery a possible thing in LABC. In addition to better control of local disease it takes care of the distant undetectable microscopic disease. Response to PST serves as a marker for long term outcome and may even help the clinician to change the chemotherapeutic agent if it appears resistant. The disadvantage is that it results in loss of assessment of well documented pathologic prognostic markers like initial tumour size, axillary lymph node involvement etc.; due to the pathological response to PST.[2,3] Thus for inoperable disease, the initial approach should be PST with the aim of achieving resectability. For operable LABC, the survival rates are equivalent for both PST and adjuvant chemotherapy if same regimen is used even in different sequence making PST a viable option.[4-7]

Most commonly used PST regimen is anthracycline containing combination chemotherapy. There is enough evidence to show the benefit from Anthracycline combination chemotherapy.[8-12] Data from RCTs show that the rate of breast conserving surgery and pathologic complete response was significantly higher for patients receiving taxanes (Docetaxel).[13-19] No consensus exists whether anthracycline and taxanes can be used in combination or in sequence.

In western countries the incidence of LABC has proportionately decreased with more use of screening mammography whereas in Indian sub-continent cases are very high. LABC is a daily challenge for surgeons and oncologists of low resources countries due to the increased incidence.[20-23] Data from various cancer registries in India reveal that the percentage advanced breast cancer patients (stage 111 & 1V together) is 50-70%. But studies on LABC are less among Indian population. Hence through this study we have tried to assess the role and adequacy of Anthracycline combination PST in down staging the disease in Indian patients. We also investigated the survival of these patients and comparing the same with existing international data.

METHODS

Patient selection

Women with primarily inoperable LABC satisfying all the following inclusion criteria were eligible for the study.

a) Female patient <75 years
b) Stage 111A (except T3N1M0), 111B, 111C
c) Tissue diagnosis of invasive Breast Carcinoma
d) Adequate Bone marrow Function- WBC >4 x 10^9/L, platelet count >100 x
e) 10^9/L, Haemoglobin >10 gm%
f) S. Creatinine <1.5 mg%.
g) S. Bilirubin, SGOT, SGPT <1.5 times the normal value.
h) Performance status – WHO 0 or 1.
i) Adequate cardiac function for the use of Anthracycline.

Patients were excluded from the study if they were detected to have the following:

1. Prior treatment for any malignancy.
2. Cardiac contraindications like history of myocardial infarction, coronary artery insufficiency and chronic congestive cardiac failure.
3. Patients with severe chronic obstructive lung disease
4. Any other medical condition which may interfere with the delivery of the planned treatment protocol. Those patients who satisfy the above said criteria were included in the study after getting their informed consent.

Pre-treatment evaluation

In our department breast cancer patients are evaluated by a clinical oncologist and surgeon. Initial evaluation of patients consisted of a detailed history taking and physical examination. After a thorough general, systemic and local examination of breast, diagnostic and metastatic work up is done. Surgeon in consultation with the Oncologist will decide whether the patient is primarily an inoperable LABC.

Tissue diagnosis were achieved in all patients with fine needle aspiration cytology (FNAC) followed by tru- cut biopsy for the hormone receptor i.e.; ER (estrogen receptor) & PR (progesterone receptor) study.

Work up include base line investigations like complete blood count, liver function and renal function tests, chest X-ray, Electrocardiogram(ECG), Ultra sonogram of abdomen, and skeletal survey .Radioisotope bone scan done only if clinically indicated. CT scan of thorax was done to rule out lung metastasis.

Cardiology evaluation includes detailed history taking, clinical examination, ECG evaluation and Echocardiogram to assess the left ventricular ejection fraction (LVEF). Patients with less than 50% LVEF were excluded. Patients were also taken up for a preanaesthetic check-up to rule out any medical contraindication for surgery. If any contraindication for surgery then they were excluded from the study.

Treatment protocol

Treatment of Locally Advanced Breast Cancer is a planned treatment. All patients who received Primary Systemic Chemotherapy with Anthracycline Combination chemotherapy FAC/ FEC (5-Fluorouracil, Doxorubicin or Epirubicin, Cyclophosphamide) satisfying the inclusion and exclusion criteria were included in study. Doses of

combination chemotherapy were 5-Fluorouracil 500 mg/m^2, Doxorubicin 50 mg/m^2 or Epirubicin 100 mg/m^2 and Cyclophosphamide 500 mg/m2 given on single day intravenously. On the start of chemotherapy the tumor size were measured as two largest perpendicular diameters. Thereafter the tumor response and operability were assessed during each visit for chemotherapy. Chemotherapy was given at 21 days interval if the haematological parameters were adequate. Chemotherapy was postponed to a maximum of 1 week if bone marrow reserve was inadequate. Granulocyte colony stimulating factors and supportive treatment were given for febrile neutropenia wherever indicated. Haematological and non haematological toxicity was assessed based on NCI common toxicity criteria. Numbers of Primary systemic Chemotherapy cycles planned were 3-4. All patients after completion of three cycles were assessed by the surgeon for operability. If operable they were taken up for modified radical mastectomy with axillary clearance (MRM+AC). If inoperable then one more cycle will be given and reassessed for surgery. If still inoperable and stable or progressive disease then taxanes were tried. Thereafter if response is inadequate for a definitive surgery then those patients were taken for simple or toilet mastectomy or radical radiation treatment. All patients after radical surgical treatment were given adjuvant chemotherapy so that total of chemotherapy cycles is six.

As previously decided all radically treated patients were taken up for local radiation treatment to chest wall and drainage areas. Radiation treatment was given in a Telecobalt machine. A total dose of 50Gy as 25 fractions was given to chest wall as two tangential fields over a period of 5 weeks. Supraclavicular fossa & axilla were treated with 50Gy as 25 fractions over a period of 5 weeks as direct on field. All patients were given 6Gy in single fraction as posterior axillary boost at the end of the 25 fractions treatment. Endocrine responsive patient (ER or PR positive) were given Tamoxifen or aromatase inhibitors as per protocol for a period of 5 years. Patients were kept on regular 3-4 monthly follow up. Follow up evaluation consisted of clinical examination to rule out local and systemic recurrences, relevant investigations were done based on the clinical findings and history. Annual mammogram was done for all patients on follow up.

Evaluation of tumor response to primary systemic chemotherapy

Response to chemotherapy was assessed both clinically and pathologically. Final clinical assessment was done by physical examination at the end of primary systemic chemotherapy. Pathological response was done on the MRM+AC specimen.

Patients were categorized as follows. A) Microscopically no residual disease- pCR (pathological complete response) B) Clinically no palpable disease- cCR (clinical complete response) C) >50% response, clinically palpable disease- CPR (clinical partial response) D) <50% response to no response – SD (stable disease).

Statistical analysis

Analysis was carried out using SPSS software with the help of medical statistician. Overall survival was calculated from start of treatment to date of death. DFS was calculated from start of treatment to date of first local or systemic recurrence. DFS and O.S was calculated using Kaplan – Meier method.

RESULTS

Table 1: Patient characteristics.

Characteristics	N =Frequency (Percentage)
Age	
<35yrs	8(10.6%)
35-44	22(29.3%)
45-54	18(24.0%)
>55yrs	27(35.9%)
Socio economic status	
Above poverty line	23 (30.7%)
Below poverty line	52 (69.3%)
Religion	
Hindus	56(74.7%)
Muslims	13(17.3%)
Christian	6 (8.0%)
Menstrual status	
Pre-menopausal	36 (48.0%)
Post-menopausal	39 (52.0%)
Parity	
Nulliparous	8(10.7%)
One	7 (9.3%)
Two	27(36.0%)
≥Three	33(44.0%)
H/O Benign breast disease	1 (1.3%)
Family H/O breast cancer in first degree relative	2 (4%)

A total of 79 eligible patients with inoperable LABC were accrued. Of this, 75 patients were finally available for assessment of response, toxicity after completion of treatment and five year survival analysis were done as per follow up details. Pre-treatment Patient characteristics are presented in Table 1. Disease characteristics- It is depicted in Table 2. Mainly Left breast was affected with disease. Majority patients presented with T4 disease. Tumour Grade 2 or 3 diseases was observed in more than 96% of patients which points towards the high risk nature. With regard to the estrogen and progesterone receptor status there is high incidence of hormone negativity. Only one fourth of the patients were both ER/PR +ve. This is significantly lower than in white women. The total hormone receptor positivity was 43.2%.The high negativity may be due to the high disease stage and high grade of tumor.

Table 2: Disease characteristics.

Characteristics	N (%)
Side affected	
Left breast	40(53.3%)
Right breast	35(46.7%)
Initial Tumour size	
<50 cm^2	38(50.6%)
50-100 cm^2	20(26.6%)
100-150 cm^2	11(14.6%)
>150 cm^2	6 (8.0%)
T status	
T3	24(32%)
T4a	3(4%)
T4b	37(49.3%)
T4c	11 (14.6%)
Lymph node status (clinical)	
N0	20(26.7%)
N1	33(44.0%)
N2	15(20.0%)
N3	7(9.3%
Pathological type	
Infiltrating ductal carcinoma	86.8%
Pure mucinous carcinoma	3.9%
Mixed mucinous carcinoma	2.6%
Lobular carcinoma	3.9%
Mixed ductal & lobular carcinoma	2 .6%
Histological Grade	
Grade one	4.0%
Grade two	69.3%
Grade three	26.7%
Receptor status	
ER+, PR+	24.3%
ER+, PR-	5.4%
ER-, PR+	13.5%
ER-, PR-	56.7%

Preoperative chemotherapy (PST): Routinely Anthracycline containing combination chemotherapy is given for locally advanced breast cancer in our institution. The most commonly used schedule is FAC followed by FEC. It is observed in this study that the average number of neoadjuvant chemotherapy cycles needed for maximum tumor response is three (Table 3).

Table 3: Details of neoadjuvant chemotherapy.

Chemotherapy	N (%)
Chemotherapy schedule	
FAC	55(74%)
FEC	20 (26%)
Number of neoadjuvant chemotherapy cycles received	
Three cycles	77.4%
Four cycles	14.1%
>Four cycles	8.4%

Clinical tumour response to primary systemic chemotherapy: In seventy five patients evaluable for response assessment a total objective clinical response was achieved in 78.9%, of which 11.3% had complete clinical response & partial response in 67.6%. With regard to the clinical nodal response the total objective response was 78% while complete clinical response was 46.3% (Table 4).

Table 4: Clinical tumour response to primary systemic chemotherapy.

Tumour response	%
Clinical response	
cCR	11.3% 13.2% (FAC) 5.5%(FEC)
cPR	67.6% 64.2% (FAC) 77.8%(FEC)
SD	21.1% 22.6%(FAC) 16.7 %(FEC)
Nodal response	
cCR	46.3% 43.3%(FAC) 54.5%(FEC)
cPR	31.7% 33.3% (FAC) 27.3%(FEC)
SD	22.0% 23.3%(FAC) 18.2% (FEC)

Surgical treatment after primary systemic chemotherapy: Primarily inoperable cases were made operable in 94.3% of cases. MRM with axillary clearance was possible in 70.4% patients. Simple mastectomy with axillary dissection in 22.5%. Only 5.6% remained inoperable in spite of the neoadjuvant chemotherapy. Microscopic clearance was achieved in 85.9% (Table 5).

Table 5: Surgery details.

Surgery	%
MRM+A.C	70.4% 73.6%(FAC) 61.1%(FEC)
Simple mastectomy+ axillary dissection	22.5% 18.8%(FAC) 33.3%(FEC)
Toilet mastectomy	1.4% 1.9%(FAC) NIL(FEC)
No surgery feasible	5.6% 5.6%(FAC) 5.6%(FEC)

Pathological response: complete pathological response was 8.0% for primary tumour and 39.4% for the nodal

disease. Postoperative margins were negative in 85.9% cases (Table 6).

Table 6: Pathological response details.

Surgical margins Negative	85.9% 86.8% (FAC) 83.3%(FEC)
Positive	14.1% 13.2% (FAC) 16.7% (FEC)
Complete pathological response Primary tumour	8.0% 9.1%(FAC) 5.0%(FEC) 39.4%
Lymph nodal response	33.3%(FAC) 45.5%(FEC)

Treatment toxicity: Both FAC & FEC had only comparable toxicity. Grade 3/4 haematological toxicity associated with FAC/FEC schedule is only 6.6% (Table 7).

Table 7: Treatment toxicity.

Type of toxicity	%
Anemia Grade 1& 2	80% 84.9% (FAC) 82.2%(FEC)
Grade 3&4	6.6% 7.4%(FAC) 5.5%(FEC)
Neutropenia Grade 1&2	74.6% 78.1% (FAC) 65.0 % (FEC)
Grade3&4	6.6% 7.4%(FAC) 5.5%(FEC)
Vomiting Grade 1 &2	76.0% 82.9% (FAC) 72.1% (FEC)
Grade 3	4.0% 3.6%(FAC) 5.5%(FEC)
Cardiac toxicity Grade 3&4	1.3% 1.8% (FAC) Nil (FEC)

Survival: 5 year OS (Figure 1) and DFS (Figure 2) of the patients were 67.92% & 62.21% respectively. Local chest wall recurrence was seen in 2.7% and nodal recurrence in 4% patients. Systemic failures were seen in 21.3% of patients.

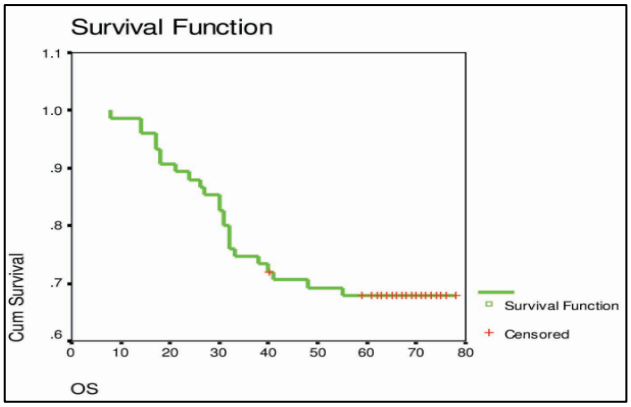

Figure 1: Overall survival.

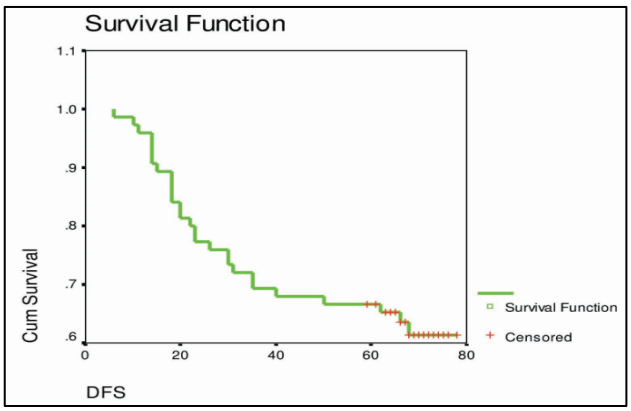

Figure 2: Disease free survival.

DISCUSSION

With the increased use of screening in developed countries, more number of patients is diagnosed in an early stage. But in many parts of the world where screening is not done routinely and locally advanced breast cancer is a clinical problem here. So any research in this area of locally advanced breast cancer will be fruitful to the community and merits priority. In the present prospective study, we have evaluated the role of Primary Preoperative systemic Anthracycline based chemotherapy in primarily inoperable LABC. Considering the different biology and clinical behaviour of inflammatory breast cancer it was not included in this study. Even though several studies have addressed this issue, in India where LABC is a real problem studies are sparse. Hence through this study we have tried to assess the response of two commonly used Anthracycline based chemotherapy i.e.; FAC & FEC and also compared the same with the western population.

The efficacy of primary systemic chemotherapy in down staging the disease and making it operable is nearly 94% in this study. A radical MRM with axillary clearance was achieved in 70.4% while simple mastectomy with axillary dissection in 22.5%. Microscopic surgical clearance achieved in 85.9% of cases. . This proves beyond doubt the role of Anthracycline based neoadjuvant

chemotherapy in loco regional control of the disease. The high percentage of radically operated patients in this study is one among the highest reported in literature. The objective clinical tumour response rate in our study was 78.9% with complete clinical response of 11.3% and partial response of 67.6%. As per literature there is large variability and heterogeneity regarding the response rate. But approximately 10-20% of patients get complete clinical response and 50-60% achieves a partial response.[24-30] Thus it proves beyond doubt the role of Anthracycline combination schedule in Indian women in tumour response.

The complete pathological response rate in this study was 8.0% whereas in several RCT in western population it ranges from 3.7% to 30%. It is observed in our study that those patients who achieved p CR have superior overall survival when compared to other patients (100% Vs 65.5%) who have not achieved it. In Taxanes based study like NSABP-27 the pCR improved significantly to 26.1%. Complete clinical nodal response rate was 46.9% & complete pathological nodal response rate was 39.4% in this study.

The toxicity profile of our study was the same as in other studies. Both FAC &FEC schedules are well tolerated. There was no significant short or long term toxicity attributable to chemotherapy.

In this study it is observed that more than 95% of patients have tumour Grade 2 or 3. Nearly 57% are Endocrine unresponsive (both ER/PR –Ve). When receptor status is compared to western population it is seen that our study group has significantly lower receptor positivity. All these biological factors point out the fact that the tumour will be more aggressive in Indian population when compared to white. In this clinical scenario newer combination schedules must be explored to overcome the aggressiveness. Since majority of Indian patients present at a very advanced stage screening must be incorporated in health programmes for early detection.

With regard to down staging of the disease and thereby achieving better local control of the disease, FAC/FEC schedule is a good option. But the p CR rates and survival outcomes of these patients are not satisfactory. The five year Overall survival was 67.92% and Disease free survival was 62.21%. The five year Overall survival as per the literature varies widely. The survival in this cohort of patients is good compared to several other studies.

Among the patients who failed majority were systemic failures, thereby pointing to the fact that this regimen is inadequate in controlling metastases. Hence newer combination schedules incorporating agents like taxanes are needed, at least in the postoperative adjuvant setting in LABC patients. So new research works addressing these issues especially in Indian setting is essential. We have also completed another study addressing the addition of taxanes in LABC patients.

Our study has limitations. It is not an RCT and only an observational study of the patients who are reporting to the department for routine treatment for LABC.

CONCLUSION

PST with Anthracycline combination agents is a reasonable standard treatment for locally advanced breast cancer in Indian population as well. It contributes to high operability of primarily inoperable LABC and even breast conserving surgery become feasible in a sizeable number of patients. Considering the aggressiveness shown by the poor endocrine responsiveness among Indian population more randomized controlled trials are warranted in this area. Breast cancer awareness and screening programmes including mammography must gain importance in Indian population and such widespread programs may bring out a revolution in early detection.

ACKNOWLEDGEMENTS

I full heartedly acknowledge Dr. P R Sasindran M.D Retired Professor for all the scientific and academic guidance he has rendered for the successful completion of this study and Dr. P K Babu, Medical statistician for the help delivered for statistical analysis.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. AJCC Cancer Staging Manual, 7th edition, 2010
2. Bonadonna G, Valagussa P, Brambilla C, Ferari L, Moliterni A, Terenziani M, et al. Primary chemotherapy in operable breast cancer: Eight-years' experience at the Milan Cancer Institute. J Clin Oncol. 1998;16:93-100.
3. Skipper HE. Adjuvant chemotherapy. Cancer1978; 41:936-40 Powles TJ, Hickish TF, Makris A et al. Randomized trial of chemo endocrine therapy before or after surgery for treatment of primary breast cancer. J Clin Oncol. 1995;13:547-52.
4. Powles TJ, Hickish TF, Makris A. Randomized trial of chemo-endocrine therapy before or after surgery for treatment of primary breast cancer. J Clin Oncol. 1995;13:547-52.
5. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998;16:2672-85.

6. Semiglazov VF, Topuzov EE, Bavli JL. Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer. Ann Oncol. 1994;5:591-5.
7. van der Hage JA, van de Velde CJ, Julien JP. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol. 2001;19:4224-37.
8. Van der Hage JA, Van de Velde CT, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: Results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol. 2001;19:4224-37.
9. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on outcome of women with operable breast cancer. J Clin Oncol. 1998;16:2672-85.
10. Cancer WG, Carey LA, Calvo BF, Sartor C, Sawyer L, Moore DT, et al. Long-term outcome of neoadjuvant chemotherapy for locally advanced breast carcinoma: Effective clinical down staging allows breast preservation and predicts outstanding local control and survival. Ann Surg. 2002;236:295-303.
11. Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, et al. Breast conservation after neoadjuvant chemotherapy: The MD Anderson Cancer Center experience. J Clin Oncol. 2004;22:2303-12.
12. Kuerer HM, Sahin AA, Hunt KK, Newman LA, Breslin TM, Ames FC, et al . Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. Ann Surg. 1999;230:72-8.
13. Heys SD, Hutcheon AW, Sarkar TK, Ogston KN, Miller ID, Payne S, et al. Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial. Clin Breast Cancer. 2002;3:S69-74.
14. Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, et al. Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel. J Clin Oncol. 2002;20:1456-66.
15. Luporsi E, Vanlemmens L, Coudert B. Six cycles of FEC 100 vs 6 cycles of Epirubicin-docetaxel (ED) as neoadjuvant chemotherapy in operable breast cancer patients (Pts): Preliminary results of a randomized phase II trial of GIREC S01. J Clin Oncol. 2000;18:19.
16. Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003;21:4165-74.
17. Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2006;24:2019-27.
18. Evans TR, Yellowlees A, Foster E, Earl H, Cameron DA, Hutcheon AW, et al. Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: An anglo-celtic cooperative oncology group study. J Clin Oncol. 2005;23:2988-95.
19. Agarwal G, Pradeep PV, Agarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. World J Surg. 2007;31:1031-40.
20. El Saghir NS, Khalil MK, Eid T. Trends in epidemiology and management of breast cancer in developing Arab countries: a literature and registry analysis. Int J Surg. 2007;5:225-33.
21. Fregene A, Newman LA. Breast cancer in sub-Saharan Africa: how does it relate to breast cancer in African-American women? Cancer. 2005;103:1540-50.
22. Rodriguez-Cuevas S, Macias CG, Franceschi D, Labastida S. Breast carcinoma presents a decade earlier in Mexican women than in women in the United States or European countries. Cancer. 2001;91:863-8.
23. Swain SM, Sorace RA, Bagley CS. Neoadjuvant chemotherapy in the combined modality approach of locally advanced non metastatic breast cancer. Cancer Res. 1987;47:3889-94.
24. Perloff M, Lesnick GJ, Korzun A. Combination chemotherapy with mastectomy or radiotherapy for stage III breast carcinoma: a Cancer and Leukemia Group B study. J Clin Oncol. 1988;6:261-9.
25. Hortobagyi GN, Ames FC, Buzdar AU. Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer. 1988;62:2507-16.
26. Bonadonna G, Veronesi U, Brambilla C. Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Nat'l Cancer Inst. 1990;82:1539-45.
27. Jacquillat C, Baillet F, Weil M. Results of a conservative treatment combining induction (neoadjuvant) and consolidation chemotherapy, hormone therapy, and external and interstitial

irradiation in 98 patients with locally advanced breast cancer (IIIA-IIIB). Cancer. 1988;61:1977-82.
28. Pierce LJ, Lippman M, Ben-Baruch N. The effect of systemic therapy on local-regional control in locally advanced breast cancer. Int J Radiat Oncol Biol Phys. 1992;23:949-60.
29. Schwartz GF, Birchansky CA, Komarnicky LT. Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. Cancer. 1994;73:362-9.
30. Fisher B, Brown A, Mamounas E. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997;15:2483-93.

Cite this article as: Anand AS. Study on the role of primary systemic chemotherapy with anthracycline combination schedule in locally advanced breast cancer: long term follow up data. Int J Res Med Sci 2015;3:3474-81.