Predicting Prognosis and Neoadjuvant Chemotherapy Response in Carcinoma Breast: A Prospective Cohort Study

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Abstract

Background:
Objective: The objectives of this study were to evaluate and quantify the response to neo-adjuvant chemotherapy by physical examination and imaging modalities.
Design: This was a prospective cohort study.
Duration: 2 years and four months i.e. from March 2012 to September 2014.
Setting: This study was conducted at Department of Surgery, KAPV Government Medical College and Hospital, Tiruchirapalli.
Participants: 30 patients with stage III breast carcinoma who were admitted at Department of Surgery, KAPV Government Medical College and Hospital.
Methods: Confirmation of diagnosis was done by FNAC/Biopsy of breast lump. Accurate measurement of breast lump was done in each patient. The patients received neoadjuvant chemotherapy (CAF regimen). Size, number and fixity of affected lymph nodes was also recorded before and after chemotherapy. The data thus collected was analysed, significance determined and the literature available was reviewed.

Results: Out of 30 patients who received neoadjuvant chemotherapy with CAF, 76.6% of them underwent down staging of tumor by one or more stages. No patient showed complete clinical resolution. 16.6% patients had <25% reduction in size of tumor, 30% patients had 25-50% size reduction, 20% patients had up to 75% size reduction and 33.3% patients had up to 99% of size reduction. All patients had palpable axillary lymph nodes, out of which, 40% showed clinical resolution, while 60% showed a change in size but not change in stage. All the patients underwent surgery.

Conclusion: Benefit from tumor down staging can be achieved by neo-adjuvant chemotherapy and it is the preferred approach for patients with bulky and locally advanced disease at the time of diagnosis.

Keywords: Carcinoma, Neo-adjuvant, chemotherapy

Introduction

Carcinoma of the breast from the very beginning has been a feared disease. Till today, there is an aura of fear that surrounds the mention of this name 'breast cancer'. The treatment modalities of carcinoma breast have come a long way after much research. Various modalities as chemotherapy, radiotherapy, hormonal therapy are present. Surgery has changed from radical ones to breast conserving surgery.

Among all modalities of treatment, surgery has come to be accepted as the 'golden standard', to which all other modalities have to be compared. Halsted's radical mastectomy has been accepted as the main factor for comparison of results of any form of treatment, that is, the results of treatment of breast cancer by any modality or a combination of to results obtained by Halsted with his radical mastectomy.

Other modalities of treatment such as chemotherapy and radiotherapy are considered as adjuvant to surgery and are incomplete by themselves. Chemotherapy has gained a greater importance ever since researchers have given breast cancer the status of a systemic disease. Surgery as such can eradicate only the local disease, and eradication of the systemic component involves the use of chemotherapeutic agents. Chemotherapy may be given as an adjuvant post operatively, or as Neo-adjuvant chemotherapy where two to three doses are given prior to surgery, followed by the remaining cycles post-operatively.

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Occasionally in very advanced cases, chemotherapy alone may be given as a palliative measure, when any form of surgery is likely to result in extensive deformity that will compromise on quality of life without a significant increase in life span.

This dissertation deals with the administration of Neo-adjuvant chemotherapy in patients who have been worked up for surgery. All patients were given three cycles of a chemotherapeutic regimen as per recommended doses, and the effect was studied three weeks after the third cycle, just prior to surgery. However, the long term follow up of patients and comparison of the 5-year survival rates and recurrence/metastasis between Neo-adjuvant and post-operative chemotherapy was out of the scope of this dissertation.

Materials And Methods

Place Of Study : This study was conducted at Department of Surgery, KAPV Government Medical College and Hospital, Tiruchirapalli.
Type Of Study : This was a prospective cohort study.
Sample Collection : Sample Size : 30 Patients
Sampling Methods : Consecutive sampling.
Inclusion Criteria : Those patients who fall under stage III (LABC) Locally Advanced Breast carcinoma were considered for the study.

Statistical Analysis : Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented as Mean ± SD and results on categorical measurements were presented in numbers (%). 95% confidence interval has been computed to find the significant features. Confidence interval with lower limit more than 50% is associated with statistical significance. Microsoft Word and Excel were used in the generation of graphs, tables etc.

Ethical Approval : Approval was taken from the Institutional Ethics Committee prior to commencement of the study.

Observations and Results

| Tumor Size (cm) | Number of patients | % |
|-----------------|--------------------|---|
| 5 - 7           | 20                 | 66.7 |
| 8 - 10          | 10                 | 33.3 |
| Total           | 30                 | 100.0 |

Table 1 : Tumor size in cm
Mean ±SD : 6.99 ± 1.39

| Lymph node involvement | Number of patients | %     | 95 % CI       |
|------------------------|--------------------|-------|---------------|
| Present                | 30                 | 100.0 | 88.65 – 100.0 |
| Absent                 | 0                  | 0     |               |
| Total                  | 30                 | 100.0 |               |

Table 2 : Lymph node Involvement
Mean ±SD : 6.99 ± 1.39

| Stage of disease | Number of patients | %     | 95% CI       |
|------------------|--------------------|-------|--------------|
| III a            | 14                 | 46.7  | 30.23 – 63.86 |
| III b            | 16                 | 53.3  | 36.14 – 69.77 |
| Total            | 30                 | 100.0 |              |

Table 3 : Stage of disease

| Stage reduction % | Number of patients | %     | 95% CI       |
|-------------------|--------------------|-------|--------------|
| <25.0%            | 5                  | 16.7  | 7.34 – 33.56 |
| 25 – 50 %         | 9                  | 30.0  | 16.67 – 47.88 |
| 50 – 75 %         | 6                  | 20.0  | 9.51 – 37.31 |
| 75 – 99 %         | 10                 | 33.3  | 19.23 – 51.22 |
| Total             | 30                 | 100.0 |              |

Table 4 : Size reduction in %

| Lymph node status | Number of patients | %     | 95 % CI       |
|-------------------|--------------------|-------|---------------|
| Down stage        | 12                 | 40.0  | 24.59 – 57.68 |
| Unchanged         | 18                 | 60.0  | 43.32 – 75.41 |
| Total             | 30                 | 100.0 |               |

Table 5 : Lymph node status
Table 6: Neo adjuvant chemotherapy

| Response to treatment | Number of patients | %    | 95% CI       |
|-----------------------|--------------------|------|--------------|
| Down staging (Partial response) | 23                | 76.7 | 59.07 – 88.21 |
| Same stage            | 7                 | 23.3 | 11.79 – 40.93 |
| Complete response (total clinical resolution) | 0                 | 0.0  |              |

Table 7: Response to neo adjuvant treatment

| Study Variables | Response to treatment | P Value |
|-----------------|-----------------------|---------|
|                 | Down staging (n = 23) | Same stage (n = 7) |
| Age in Years    |                       |         |
| 31 - 40         | 2 (8.7%)              | 1 (14.3%) |
| 41 - 50         | 6 (26.1%)             | 2 (28.6%) |
| 51 - 60         | 12 (52.2%)            | 3 (42.9%) |
| >60             | 3 (13.1%)             | 1 (14.3%) |
| Tumor size (cm) |                       |         |
| 5 - 7           | 15 (65.2%)            | 5 (71.4%) |
| 8 - 10          | 8 (34.8%)             | 2 (28.6%) |
| Stage of disease|                       |         |
| III a           | 13 (56.5%)            | 1 (14.3%) |
| III b           | 10 (43.5%)            | 6 (85.7%) |

Table 8: Correlation of study variables with response to treatment

| Stage reduction % | Number of patients | %    | 95% CI     |
|-------------------|--------------------|------|------------|
| <25%              | 5 (16.7%)          | 1 (7.1%) | 4 (25%)    |
| 25 – 50%          | 9 (30.0%)          | 5 (35.7%) | 4 (25%)   |
| 50 – 75%          | 6 (20.0%)          | 5 (35.7%) | 1 (6.3%)  |
| 75 – 99%          | 10 (33.3%)         | 3 (21.4%) | 7 (43.8%)  |
| Total             | 30 (100%)          | 14 (100%) | 16 (100%) |

Inference: Higher size reduction is positively associated with IIIB stage of disease with p = 0.126

Table 9: Correlation of size reduction in % with stage of disease

Discussion

This dissertation deals with the study of breast cancer patients who were admitted at KAPV GOVT. Medical College Hospital and received anterior chemotherapy. A total of 30 patients who presented in stage III were included in the study during the period May 2012 to Sep 2014. Most common stage at presentation in Indian Population is stage III. In our study we have included only the patients who have presented with stage III. 30 patients with locally advanced breast cancer received 3 cycles of Neo-adjuvant chemotherapy with Cyclophosphamide, Adriamycin and 5 with fluorouracil.
All the patients treated in this manner were seen to show good response to chemotherapy. Out of 30 patients who received Neo-adjuvant chemotherapy with CAF, 76.6% of them underwent down staging of tumor by one or more stages. Results of NSABP B-18 (National Surgical Adjuvant Breast Project) on the effect of preoperative chemotherapy, 36% of patients obtained a clinical complete response and 43% of patients obtained a clinical partial response, for an overall response rate of 79%\(^2,3\). These patients were closely monitored to effect of these drugs on the tumor, lymph nodes and other metastasis if present.

All patients in this study had clinically palpable tumors. All the tumors have responded to anterior chemotherapy with a decrease in size. Resistance to chemotherapy was not encountered in the course of the study. No patient showed complete clinical resolution. In NSABP B-18 trails 13% of the patients achieved a pathologic complete response (absence of invasive tumor in the breast specimen following neo-adjuvant chemotherapy).

| Size Reduction | No. of patients | Percentage |
|----------------|-----------------|------------|
| <25%           | 5               | 16.6%      |
| 25 – 50 %      | 9               | 30%        |
| 50 – 75%       | 6               | 20%        |
| 75 – 99 %      | 10              | 33.3%      |

Table 10: Depicts response of neo-adjuvant chemotherapy in percentage of tumor size reduction.

Out of 30 patients who received neo-adjuvant chemotherapy 16.6%Patients have <25% reduction of size of tumor, 30% of patients have 25-50% size reduction, 20% of patients have up to 75% size reduction, 33.3% of Patients have up to 99% of size reduction. All patients had palpable axillary lymph nodes, out of which, 40% showed clinical resolution, while 60% showed a change in size but not Change in stage. No patient had increase in lymph node stage. In NSABP B-18 trial administration of preoperative chemotherapy resulted in significant pathologic axillary lymph node down-staging in 37% of the patients presumed to be node-positive at the time of administration of preoperative chemotherapy\(^2, 3\). In our study no patient developed findings of fresh metastasis during the course of Neo-adjuvant Chemotherapy. All the patients who received Neo-adjuvant Chemotherapy underwent surgery. Von Minckwitz and Colleagues reported in 2005 that early response to induction chemotherapy within the first one to two cycles can identify those patients who will have a high likelihood of achieving complete pathologic response.

| Studies       | Down Staging % |
|---------------|----------------|
| Out Study     | 76.6%          |
| NSABP B-18    | 79%            |

Table 11: Clinical Overall Response

Conclusion

Patients with stage III Breast Cancer will benefit from tumor down staging. Neo-adjuvant Chemotherapy is preferred for down staging the tumor and lymph nodes. Delaying the surgery while systemic therapy is being delivered does not upstage the disease. Tumor response to neo-adjuvant chemotherapy is more compared to the lymph nodal response. Benefit from tumor down staging can be achieved by Neo-adjuvant chemotherapy and it is the preferred approach for patients with bulky and locally advanced disease at the time of diagnosis.

References

ICMR. National Cancer Registry Programme, 2001-2004, Development of an Atlas of Cancer, Chapter 3, Cancer incidence and leading sites of cancer in population based cancer registries.
Andresen TI, Heimdal KR, Skrede M, et al. Oestrogen receptor (ESR) polymorphisms and breast cancer susceptibility. Hum Genet 1994;94(6):665-70.
Roodi N, Bailey LR, Kao WY, et al. Estrogen receptor gene analysis in estrogen receptor-positive and receptor-negative primary breast cancer. J Natl Cancer Inst 1995;87(6):446-51.