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ORIGINAL ARTICLE

Measurement of Residual Breast Cancer Burden after Neoadjuvant Chemotherapy

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ABSTRACT

Aim: To determine the frequency of residual cancer burden after neoadjuvant chemotherapy for breast cancer patients undergoing surgery.

Study Design: Descriptive study.

Place and Duration of Study: Department of Surgery, Dr. Ruth K.M. Pfau Civil Hospital Karachi from 8th May 2019 to 7th November 2019.

Methodology: One hundred and twenty six females aged 25 to 75 years with stage IIA, IIB and IIIA were enrolled. Patients who had received standard protocol of neoadjuvant chemotherapy from outside i.e. six cycles of fluorouracil, anthracycline and cyclophosphomide (FAC) every 3 weeks and for HER2+ tumors, FAC was followed by 12 cycles of Trastuzumab every 3 weeks were included. Data regarding tumor characteristic, age, HER 2 status, PR status, KI 67status and nodal involvement was noted.

Results: The mean age was 47.32±13 years and mean cancer cellularity was 14.88±10.4%. Nuclear grade III was present in 39.7% patients and 48.4% patients belonged to T1 stage. Majority of patients were menopausal. FAC regime was used in 58.7% patients. RCB I (minimal residual disease) was present in 12.7% patients, RCB II (moderate residual disease) was present in 51.6% patients and RCB III (extensive residual disease) was found in 35.7% patients. Cross tabulation for age, T stage, pathological AJCC classification, histological classification and nuclear grading was not significant (p>0.05).

Conclusion: Neoadjunctive therapy is associated with decrease rate of residual cancer burden.

Keywords: Breast carcinoma. Neo adjunctive therapy, Decreases residual cancer burden

INTRODUCTION

Breast cancer is the most common cancer among females around the globe and Pakistan has been facing rising incidence in number of cases in the recent years.[1,2] Neoadjuvant therapy now plays a key role in the multidisciplinary management of breast cancer.[3] Pathological complete response achieved after chemotherapy is an autonomous factor in the long term survival of patients and is considered as the final goal of neoadjuvant trials.[4] Pathological complete response is associated with no residual disease present. By combining the histopathological components of residual disease including the cellularity, overall diameter, number and extent of lymph node involvement an index was formed that calculates the residual cancer burden (RCB).[5] Long term survival of breast cancer patients after surgery can be effectively evaluated with RCB.[6]

Neoadjuvant therapy is now the recommended therapy for locally advanced cancers, tumors that are too large to be removed surgically.7 Patients have shown improvement in pathological complete response after advances in treatment in neoadjuvant trials.[8] The regimen of drugs used for chemotherapy is itself an independent factor in achieving pathological complete response.

Neoadjuvant therapy is a new therapeutic intervention that proves greatly effective against down staging breast tumors. It helps in monitoring of tumor response against therapy and for the identification of markers against adjuvant therapy. Alternatively Miller and Payne classification takes into account only decrease in cancer cellularity after Neoadjuvant chemotherapy and ignore nodal status and tumor size completely.[9] However it has been shown that cancer cellularity and tumor size are directly related and reduction in cellurarity depends upon tumor size as well. Residual cancer burden in previous research was calculated as 20.6%.[5] Residual cancer burden calculations will provide a better view of pathological complete response, the extent of residual disease and defining patients of breast cancer with near pathological complete response or resistance.

Data on residual burden evaluated after operating for breast cancer in patients who have received neoadjuvant chemotherapy is not available from our part of the world. There is no evidence based study at present that calculates the percentage of residual breast cancer burden. This study was provide a better view of residual cancer burden that have an impact on overall survival of patients which in turn has an effect on the life expectancy in breast cancer patients and decrease in morbidity and mortality.

MATERIALS AND METHODS

This descriptive study was conducted at Department of Surgery, Dr. Ruth K.M. Pfau Civil Hospital Karachi from 8th May2019 to7th November 2019 and 126 breast cancer patients were enrolled. Female patients with age 25-75 years and breast cancer patients diagnosed as Stage IIA (T1, N1, M0or T2, N0, M0), IIB (T2, N1, M0 or T3, N0, M0), or IIIA (T1–2,N2, M0 or T3, N1–2, M0) who have received six cycles of Fluorouracil, anthracycline and cyclophosphomide (FAC) every 3 weeks and for HER2+ tumors, FAC was followed by 12 cycles of T rastuzumab every 3 weeks and are undergoing surgery were included. Stage 4 breast cancer, recurrent breast cancer, synchronous cancer at site other than breast, not fit for surgery and sentinel lymph node biopsy carried out before administration of neoadjuvant chemotherapy were excluded. Brief clinical history was taken and physical examination was done. All breast cancer patients were staged by examination, U/S or Mammography, Bone Scan, CT scan chest and biopsy. They were sent for neoadjuvant chemotherapy (six cycles of Fluorouracil, anthracycline and cyclophosphomide (FAC) every 3 weeks and for HER2+ tumors, FAC was followed by 12 cycles of Trastuzumab every 3 weeks) for shrinkage of tumors. After chemotherapy they were operated and postoperative specimen sent for histopathology to find the residual disease burden by RCB calculator. Demographic and clinical data regarding age (years), Pre/postmenopausal status, ER status, PR status, Her 2, ki67 status was noted. Tumor characteristics before treatment including lymph node status, clinical tumor size and clinical AJCC stage were noted. Group of Neoadjuvant Chemotherapy Regimen FAC or FAC + Herceptin was noted. After recording the details, patients were prepared for surgery (modified radical mastectomy or breast conservative surgery) depending upon the indication. After surgery the specimen was sent for histopathology to look for following parameters: Tumor size, pathological AJCC stage, histological sub-type, size of the tumor bed, overall cancer cellularity, percentage of

cancer that is in situ stage, No. of positive lymph nodes and the diameter of largest lymph node metastasis, nuclear grade. Residual tumor burden was calculated by placing the required variables in the web based calculator. All the data was entered and analyzed through SPSS-20.

RESULTS

The mean age was 47.32±13.67 years and mean cancer cellularity was 14.88±10.4 (Table1). Majority of patients had nuclear grade 3 i.e. 39.7%. There was no nodal involvement in 22.2%patients. T1 stage was present in 48.4% patients. More patients belonged to III-A pathological classification i.e. 39.7. On histological classification invasive ductal carcinoma was present in majority of patients 35.7%. 52.4%females were post-menopausal. ER status was positive in 58.7% population. PR status was positive in 65.1%. HER2 was present in 23.8%. KI67 was positive in 23.8% females. FAC regime was used in 58.7%patients. FAC + Herceptin regime for Her2 +ve tumors were used in 41.3% patients. Sixty five (51.6%) patients had RCB II followed by RCB III in45 (35.7%) patients (Table2).

Table1: Descriptive statistics of the post-neoadjuvant chemotherapy

Variable	Mean±SD
Age (years)	47.32±13.67
Tumor size width (mm)	16.08±10.246
Tumor size length (mm)	28.57±11.56
Cancer cellularity (%)	14.88±10.47
Diameter of largest lymph node (mm)	14.98±12.35
Percentageofinsitu cancer(%)	19.61±21.38

DISCUSSION

In our study residual cancer burden is evaluated after operating for breast cancer in patients who had received neoadjuvant chemotherapy. No evidence based study was previously available that could calculate the percentage of residual breast cancer burden. Our study was provided a better view of residual cancer burden that carry an impact on overall survival of patients and further helpful in increasing the life expectancy in breast cancer patients and in turn decreasing morbidity and mortality.

The mean age of sample population was 47.32±13.67 years, mean cancer cellularity was 14.88±10.4. Majority of patients had nuclear grade 3 i.e. 39.7%. There was no nodal involvement in 22.2%patients. T1 stage was present in 48.4% patients. More patients belonged to III-A pathological classification i.e. 39.7%. On histological classification invasive ductal carcinoma was present in maximum number of patient i.e. 35.7%. 52.4% females were post-menopausal. ER status was positive in 58.7 % population. PR status was positive in 65.1%. HER 2 was present in 23.8%. KDI 67 was positive in 23.8% females. FAC regime was used in 58.7% patients. Majority of patients had RCB II. Cross tabulation for age, T stage, pathological classification, histopathology subtype and nuclear grade was not significant. Our results are supported by other international studies. Symmans et al[10] selected total 219 patients with 52% of II-A stage, HER 2 was positive in 23% patients and maximum patients had RCB I and RCB II after neoadjunctive chemotherapy 32% in each group. Peintinger et al[11] also conducted study on 199 patients all having HER2 positive and used neoadjunctive chemotherapy. The median age was 48 years close to median age of our study with maximum patients in T2 category i.e. 61 % while our patients mostly had T1 category and maximum patient had 1 node involvement like our study. 36% patients had II-AAJCC stage. This study has baseline characteristic similar to our study and results were comparable i.e. RCBI was present in 18% and RCBII was present in 22%. All these results validate the data of our study.

Chatterjee and Erban[7] reported the benefit of down staging tumor size using neoadjuvant chemotherapy, there may be special considerations in the cases where breast size is larger and tumor is large (e.g. T2-T3 invasive cancer) breast cancer, neoadjuvant chemotherapy should certainly to reduce tumor size and facilitate breast conservation and decrease the residual cancer burden post operatively. Hence it is proved that our results are comparable with international data and can be used as guideline for treatment of breast carcinoma patients.

Table 2: Demographic information of the patients

Variable	No.	%
Nuclear grade		
1	44	34.9
2	32	25.4
3	50	39.7
Lymph node involvement		
5	9	7.1
4	5	4.0
3	13	10.3
2	38	30.2
1	33	26.3
No	28	22.2
T staging		
T0	32	25.4
T1	61	48.4
T2	20	15.9
T3	13	10.3
Pathological classification		
II-A	11	8.7
II-B	35	27.8
III-A	50	39.7
III-B	12	9.5
III-C	12	9.5
IV	6	4.8
Histological subtypes		
Insitu ductal carcinoma	28	22.2
Insi tulobular carcinoma	12	9.5
Invasive ductal carcinoma	45	35.7
Invasive lobular carcinoma	17	13.5
Invasive tubular carcinoma	18	14.3
Invasive medullary carcinoma	6	4.8
Menopausal status		
Pre-menopausal	66	52.4
Post-menopausal	60	47.6
ER Status		
Positive	74	58.7
Negative	52	41.3
PR Status		
Positive	82	65.1
Negative	44	34.9
HER-2 Status		
Positive	30	23.8
Negative	96	76.2
KI 67 Status		
Positive	30	23.8
Negative	96	76.2
Neo-adjunctive regime		
FAC	74	58.7
FAC + Herceptin	52	41.3
Residual cancer burden		
I	16	12.7
II	65	51.6
III	45	35.7

CONCLUSION

The neoadjunctive treatment is associated with increased frequency of RCB I and RCB II, while RCBIII had decreased frequency after neoadjunctive treatment. Residual Cancer is decreased in patients undergoing chemotherapy. Thus neoadjuvant chemotherapy increases the disease free survival with decrease in recurrence.

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