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Original Article

Choosing Wisely – Implication based on Indian data in our patients with breast cancer (INR vs. USD)

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ABSTRACT

Objectives: Breast cancer is increasing in India due to aging population, better awareness among general public, willingness to seek treatment of cancers, and easier access to cancers centers. We present our single-center data over a 2-year period and discuss cost implications taking the example of metronomic chemotherapy maintenance and predictive markers in early breast cancer.

Material and Methods: Prospectively collected data of all consecutive patients with breast cancer registered between September 2017 and August 2019 were evaluated. Clinical features, stage, receptor status, and other features were tabulated. Statistical analysis was using SAS version 9.4 – Chi-square test and Fisher's exact test were performed. $P \leq 0.05$ was considered as statistically significant.

Results: For the 484 consecutive patients, the median age was 50 years. This included EBC (201, 42%), LABC (141, 29%), and MBC (142, 29%). ER expression was seen in 52% of cases (253/484), PR in 47% (229/484), and Her2 was positive in 47% (229/484). Finally, 83 patients (17%) were identified as TNBC. HR-positive Her2-negative EBC constituted 111/484 patients (23%).

Discussion: If our 83 TNBC patients were given metronomic maintenance chemotherapy, their 3-year overall survival (OS) is projected to increase from 54% to 100% at a cost of INR 8191/- per patient (equivalent to USD 109/-). If our 111 HR-positive Her2-negative EBC patients were evaluated for risk by biomarker test validated in Indian patients, 76 of these would be spared the toxicity of adjuvant CT. This would also result in saving on the cost of chemotherapy medication of INR 4,035,296/- in India (equivalent to USD 53,699/- if treated in USD). In addition, they would also have better quality of life (QoL).

Conclusion: It is possible to identify patients with low risk early breast cancer using Can assist and save them from unnecessary cost and/or toxicity.

Keywords: Cost implications, Toxicity, Overtreatment, Metronomic chemotherapy, Maintenance

INTRODUCTION

Patients with breast cancer are increasing in India (like other parts of the world) due to a combination of various factors – actual increase in the incidence, aging population, better awareness among general public, willingness to seek treatment of cancers, and easier access to cancers centers.[1,2] We have previously published our data on 370 consecutive patients with breast cancer seen at our center from August 2015–2017.[3] We now present our data for the subsequent 2-year period and discuss how we can wisely use published Indian data to choose the right treatment option in our patients with breast cancer. We have then taken Indian publications to evaluate cost implications of metronomic chemotherapy maintenance in triple

negative breast cancer (TNBC) and predictive biomarker testing to avoid chemotherapy in low-risk hormone receptor (HR)-positive Her2/neu (Her2)-negative early breast cancer (EBC).

MATERIAL AND METHODS

Prospectively collected data of all consecutive patients with breast cancer of infiltrating duct carcinoma (IDC) type at the Bhagwan Mahaveer Cancer Hospital and Research Center, Jaipur (Rajasthan), registered between September 2017 and August 2019 were evaluated, retrospectively. Data regarding age, menopausal status and lymph node positivity, and site of tumor were specifically focused upon. Tumor biopsy reports of estrogen receptor, progesterone receptor, and Her2 testing were also tabulated. It was our hospital's policy to do Her2 testing by immunohistochemistry (IHC) first and fluorescent *in situ* hybridization (FISH) was done only when necessary.

American tumor-node-metastasis (AJCC TNM) staging seventh edition was used to divide patients into early breast cancer (EBC; Stage I, IIA, or IIB disease with T2N1), locally advanced breast cancer (LABC; Stage IIB with T3N0, IIIA or IIIC), and metastatic breast cancer (MBC; Stage IV).[4]

Patients were also divided into two age groups, those 50 of age or younger and those above the age of 50 years. Data were statistically analyzed using SAS version 9.4. For categorical data, "Chi-square test" and "Fisher's exact test" were performed. $P \leq 0.05$ was considered as statistically significant.

RESULTS

There were a total of 484 consecutive breast cancer patients diagnosed at our center over the 24-month period between September 2017 and August 2019. The median age was 50 years with a range from 26 to 88 years (256 patients 50 years or younger; 228 above the age of 50 years). Premenopausal patients numbered 171 and 313 were postmenopausal. Correlation between age and menopausal status is shown in Table 1.

The right-sided breast cancer was diagnosed in 49% (236/484) of patients and the tumor was on the left side in 51% (245/484). Interestingly, three patients presented with bilateral breast cancer.

At the end of the diagnostic investigations, patients were divided into EBC (201, 42%), LABC (141, 29%), and MBC (142, 29%) using the 7th AJCC breast cancer stating criteria.[5]

The axillary lymph node (LN) status of the 342 non-metastatic (EBC + LABC) is shown in Table 2. A total of 108 patients (47%) did not have any axillary LN involvement. Another 108 had 1 to 4 axillary LN showing metastasis. The remaining 73 patients had more than 4 axillary LNs involved by the cancer.

ER expression was seen in 52% of cases (253/484), PR in 47% (229/484), and Her2 was positive in 47% (229/484) [Figure 1]. For the 26 patients whose Her2 status was equivocal by immunohistochemistry (IHC), fluorescent *in situ* hybridization (FISH) was able to clearly identify 23 as Her2 negative and the remaining 3 as Her2 positive.

Finally, 83 patients (17%) were identified as TNBC [Table 3]. Their median age was 46 years and 59% (49/83) were aged 50 years or lower. Of these 83 TNBC, 38 did not have involvement of the axillary LNs.

Among the 201 EBC patients, 111 (55%) were ER positive as well as Her2 negative [Figure 2].

DISCUSSION

Our patients with breast cancer have not changed much over the 4-year period from 2015 to 2019 [Table 4]. This would indicate that breast cancer pattern has remained stable at our

Table 1: Age versus menopausal status.

	Pre menopausal	Post menopausal	Total
Age ≤ 50 years	169	87	256
Age > 50 years	2	226	228
Total	171	313	484

Table 2: Axillary LN status in non metastatic (EBC+LABC) patients.

Axillary LN involvement	*n* =	%	Age range	Age median
Zero	161	47.08 %	30 to 88	52
1 to 4	108	31.58 %	26 to 80	50
> 4	73	21.34 %	28 to 78	48
Total cases	342	100 %		

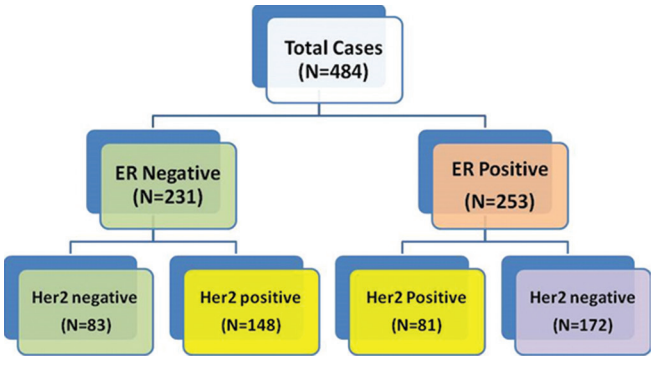

Figure 1: ER and her 2 status.

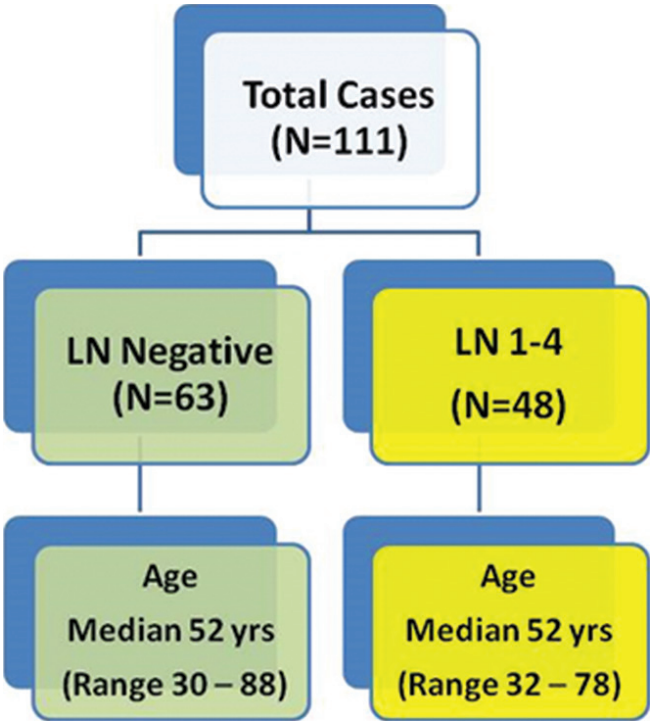

Figure 2: Selected features of ER +ve, Her 2 −ve EBC patients.

Table 3: Triple negative breast cancer patients (*n*=83/484).

Age	
Median	46 years
Range	29 to 78 years
≤ 50 yrs	49 (59 %)
> 50 yrs	44 (41 %)
Axillary LN Status	
Negative	38
Positive	45

Table 4: Comparison of selected clinical and biomarker characteristics between the two consecutive time cohorts

	2015–17	2017–19
Age		
40 years or less	21 %	17
41–60 years	61 %	64
More than 60 years	18 %	19
N =	470	484
ER positive	50 %	52
PR positive	47 %	47
Her2 positive	50 %	48
TNBC	17 %	17

center.[3] However, cost of treatment remains a continuing challenge, in India and globally.[6,7] Let us take the example of trastuzumab. In India, its use for 9 weeks is cost effective but not for 1 year (at the current price).[6] And globally, efforts to find evidence that shorter durations of trastuzumab are not inferior continue.[7]

TNBC

Our incidence of TNBC (17%) is similar to that reported from the west (15%) and contrary to other reports from India.[8]

TNBC is said to be a disease with poor prognosis, suboptimal response to therapy and therefore is a disease with unmet needs.[9-11]

Various biomarkers such as circulating tumor cells, cell-free DNA, and PD-L1 expression as well as novel therapeutic agents have been studied.[12-15]

Till they become standard of care, is there a way of improving the survival in patients with TNBC? Banavali *et al*. studied the role of maintenance metronomic chemotherapy in a prospective randomized study in Indian patients with TNBC.[16]

All patients received six cycles of standard cyclophosphamide, adriamycin, and 5-fluouracil (CAF). They were then randomized to observation versus metronomic maintenance therapy (MMT) [first 12 weeks of daily oral celecoxib 200 mg BD, daily oral cyclophosphamide (50 mg OD) and weekly IV cisplatin (25 mg/m^2)]; followed by 1 year of daily oral metformin (500 mg BD), daily oral cyclophosphamide (50 mg OD), and weekly oral methotrexate (12 mg/m^2). The cost of such MMT would be Rs. 8191/- per patient [Table 5] equivalent to 109/- USD if treated in India.[17-19]

Banavali *et al*.'s data showed that the 3-year overall survival (OS) was 100% in the MMT arm versus 54.3% in the observation arm.

If our 83 TNBC patients were all given the above MMT, 38 more patients would have survived for 3 years at the total cost of Rs. 679,853/- (Rs. 8191 per patient × 83 patients). This would translate into Rs. 5964/- per life year per patient (USD 79.6 per added year of life per patient if treated in India). If these same patients were treated in the USA, the cost would be USD 7673/- per patient and USD 636,859/- for 83 patients. This would translate into USD 5587/- per life year per patient.

HR-positive Her2-negative EBC

Of the 201 patients with EBC, 111 (55%) were HR positive as well as Her2 negative. There is a lot of interest in deciding which of these should get adjuvant chemotherapy.[20] The objective is to identify real high-risk patients and only offer CT to this subset. In addition to clinical features, the only biomarker test studied sufficiently in Indian patients is CanAssist Breast.[21,22] As per ICMR guidelines, in routine clinical practice, we should only use tests that have been validated in Indian patients.[23] This is because there is

Table 5: Cost in India and the USA of full course of metronomic maintenance therapy (MMT) per patient of TNBC

Medication	Dose for SA 1.67 m2	No. of doses	Price per dose in India	Price per dose in the USA	Total price in INR in India	Total price in USD in the USA
First 12 weeks						
Celecoxib	200 mg	168	6.90	1.87	1159.20	314.16
Cyclophosphamide	50 mg	84	2.67	0.60	224.28	50.40
Cisplatin	50 mg	12	262.78	492.50	3153.36	5910.00
Next 1 year						
Metformin	500 mg	730	1.42	0.08	1036.60	58.4
Cyclophosphamide	50 mg	365	2.67	0.60	974.55	219.00
Methotrexate	20 mg	52	31.6	21.56	1643.20	1121.12
Total Price in India versus USA					INR 8191/- (equivalent USD 109/-)	(equivalent INR 576,607/-) USD 7673/-

Table 6: Cost in India and the USA of full course of doxorubicin cyclophosphamide (AC) followed by paclitaxel (T) adjuvant CT per patient with early breast cancer.

Medication	Dose for SA 1.67 m2	No. of doses	Price per dose in INR in India	Price per dose in USD in the USA	Total price in INR in India	Total price in USD in the USA
First 4 cycles						
Doxorubicin	100 mg	4	2170	58.24	8680	232.96
Cyclophosphamide	1000 mg	4	154	231.01	616	2464.00
Next 4 cycles						
Paclitaxel	300 mg	4	10,950	55.70	43,800	222.80
Total					INR 53,096/- (equivalent USD 707/-)	(equivalent INR 219,293/-) USD 2920/-

evidence of biological and genetic variations among ethnic and geographically diverse groups – a fact that has been acknowledged by 74% (n = 137/185) of participants in an online survey (personal communication Dr. Purvish M. Parikh). Among the HR-positive Her2-negative EBC patients in India, CanAssist Breast results have shown that 68% are low risk for recurrence (and should not be given chemotherapy), whereas the remaining 32% are at high risk of recurrence (and are candidates for adjuvant CT).[24] Another survey among Indian oncologists showed that the preferred chemotherapy in this setting is adriamycin-cyclophosphamide (AC) followed by paclitaxel[25]. The cost of such adjuvant CT would be Rs. 53,096/- per patient [Table 6] equivalent to 707/- USD.

Among our 111 patients, this would mean that 76 patients would be spared the toxicity of adjuvant CT and 35 would benefit from it.

By avoiding overtreatment in 76 patients, the saving on the cost of chemotherapy medication itself would be INR 4,035,296/- (equivalent to USD 53,699/- if treated in India and USD if treated in the USA). In addition, there would be a substantial benefit of maintaining quality of life (QoL) by avoiding potential toxicity.

In summary, it is time to choose wisely. We discussed two important groups of breast cancer – TNBC and HR-positive Her2-negative EBC. This was possible because we now have the advantage of robust data from our own patients. Thus, it is possible to ascertain the implications of treatment options selected, discuss details with the patients, and arrive at the final treatment plan taking into consideration patient preferences.

CONCLUSION

It is possible to identify patients with low risk early breast cancer using Can assist and save them from unnecessary cost and/or toxicity.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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