Journal of Cancer Science & Therapy - Open Access

JCST/Vol.1 Issue 2

Research Article | OPEN ACCESS Freely available online | doi:10.4172/1948-5956.1000013

Clinical Studies on Hormonal Status in Breast Cancer and its Impact on Quality of Life (QOL)

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Abstract

Breast cancer is a steroid hormone–dependent tumor. Stratification of patients according to hormone (ER/ PR) receptor status and nodal metastasis is of great therapeutic importance. In this investigation, we could enroll 79 pre and post-menopausal breast cancer patients voluntarily. We classified these cases into four categories of the combinations of ER/PR positive, negative and mixed statuses. Their hormone receptor status as determined by immunohistochemistry correlated with therapy regimens like chemotherapy, hormone therapy and QOL responses. We found that in ER^+/PR^- and ER^-/PR^- tumors were more frequent in postmenopausal women than ER^+/PR^+ tumors. The ER^+/PR^- tumors were larger than ER^+/PR^+ tumors. In addition, 21.51% of ER^+/PR^- and 17.72% of ER^-/PR^- patients had four or more axillary nodes involved with tumors compared to patients with ER^+/PR^+ tumors (7.59%). Postmenopausal women with ER^+/PR^- and ER^-/PR^- who received adjuvant hormonal therapy or combination of chemo drugs like Cyclophosphamide, Adriamycin, 5-FU (FAC) and Cyclophosphamide, Alurubicin, 5-FU (CAF) showed good response than premenopausal women. Forty patients receiving tamoxifen (hormone therapy) along with other chemo- drugs also showed good response. Tamoxifen induced substantial tumor regression and increased disease free survival. It is concluded that hormone receptor status is important in deciding the choice of treatment for all subgroups and influenced the QOL. Another significant observation was that the frequency of ER^+/PR^- and ER^-/PR^- tumors was higher in this study group compared to ER^+/PR^+ tumors. This is the first report from south Indian population indicating the importance of hormonal status in deciding therapeutic regimens in breast cancer patients affecting their QOL.

Keywords: Breast cancer; Estrogen and progesterone receptors; QOL (quality of life); Tumor grade; Nodal status; Chemotherapy; Tamoxifen

Introduction

The importance of hormone status in breast cancer patients is because estrogen and progesterone are the key determinants of the therapy. Estrogen (ER) and progesterone (PR) can increase both normal and abnormal breast cell growth. Estrogen and progesterone receptors are highly predictive of breast cancer that will benefit from endocrine therapy. The ER is a nuclear receptor protein that has an estrogen-binding domain and a DNA-binding domain. The ER complex binds directly to the DNA and regulates the expression of other genes including the PR. The PR is a heterodimer encoded by a single gene (Rayter, 1991). ER and PR are specific receptors for estrogen and progesterone occurring in hormone-dependent organs, and can be expressed or over expressed in a variety of malignant tissue. Presently, Immunohistochemistry (IHC) routinely determines a tumor's ER/ PR status. The prognostic characterization of breast cancer patients is generally and/or routinely done on clinico-pathological parameters such as stage, histology, grade on the residual tumor after surgery, this diagnosis appears to be inadequate, since patients with similar clinicopathological characteristics often experience different clinical outcome affecting their QOL. Only a few proven biomarkers of breast cancer progression were clinically useful (Pichon et al., 1996). Therefore, the identification of more biological biomarkers related to tumor aggressiveness could be relevant in order to identify patients with different prognosis to increase their chances to respond to chemotherapy. This allows selection for high-risk patients needing therapy that is more aggressive or alternative treatment at the time of initial diagnosis, and a closer follow-up of their QOL. The QOL of patients is now becoming a very important indicator of diagnosis that can be easily determined by using a structured questionnaire and analyzing the data statistically.

In addition, breast cancer affects women's identities and therefore studying quality of life in women who lose their breasts is vital. In addition, it is known that women play an important role in family, thus when a woman develops breast cancer all family members may have some sort of apprehensions to develop some illnesses. Thus, the matter of 'survivorship' has now become an important topic in breast cancer care that demands the investigation of long-term effects of breast cancer diagnosis and treat-

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Received November 06, 2009; **Accepted** December 28, 2009; **Published** December 28, 2009

Citation: Jamil K, Kumar K, Fatima SH, Rabbani S, Kumar R, et al. (2009) Clinical Studies on Hormonal Status in Breast Cancer and its Impact on Quality of Life (QOL). J Cancer Sci Ther 1: 083-089. doi:10.4172/1948-5956.1000013

ment. Although several epidemiological and in vitro studies have demonstrated that, similar to endometrial cancer and ovarian cancer, cell biology appears to influence the biochemical pathways, promoted by the interaction of hormones with their specific receptors. Conflicting data about the possible clinical role of ER and PR in this neoplasm has been reported. Our earlier studies on the polymorphic genes in breast carcinomas (Kumar and Jamil, 2006; Kumar et al., 2007; Khan et al., 2007) indicated that these polymorphic sites are important with respect to progression of the disease, and the genotypes were useful indicators of dose- response to therapies (Suman and Jamil, 2006; Khan and Jamil, 2008). Among the biological parameters proposed as possible prognostic factors in breast cancer, focus is on endocrine factors, especially on steroid hormones and their receptors (Scambia et al., 1998).

The status ER and PR of breast cancer predicts a patient's response to clinical course like hormonal manipulation and select patients for adjuvant systemic therapy. However, there is controversy on the value of ER or PR status, separately, as prognostic indices and for their use in the selection of patients for adjuvant therapy (Clark et al., 1983). Predictive power enhances the ER and PR statuses when considered jointly. For example, tumors that are both ER+ and PR+ (approximately 70% of breast tumors) show better response to either additive or ablative endocrine therapy, whereas tumors which are ER-PR- show poorer response (approximately 10% of tumors) and tumors that are discordant for ER and PR show an intermediate response, irrespective of which receptor is positive (Wittliff, 1984).

In view of the conflicting results, we carried out investigations on hormonal (ER and PR) status in pre and post-menopausal breast cancer cases and objectively evaluated for prognostic biomarkers. In this retrospective study, we have also tried to determine and correlate the frequency of hormonal status and QOL in this group of patients, since it is becoming clear that the presence of the classical ER status is insufficient to recommend for anti-estrogen treatment and the absence of ER is not sufficient to recommend against anti-estrogen therapy.

Materials and Methods

Study approval

The Responsible Committee for Human studies and the Institutional Ethical committee, before its commencement, approved the study. The study group gave signed Informed consent. We used a 'Structured Questionnaire' to collect information on socio-demographic factors, reproductive and menstrual histories, hormone use, alcohol consumption, cigarette smoking, recreational exercise, medical history, and family history of breast cancer. Interviewers measured height, weight and recorded age of all participants.

Study group

The study group consisted of premenopausal and postmenopausal women with about 25-76 years of age diagnosed as invasive breast carcinoma [IDC] mostly in Mahavir Hospital and Research Center, Hyderabad, and other hospitals (MNJ, IACI&RC), all were residents of Andhra Pradesh (South India). Cases diagnosed between June 2008 to June 2009 were selected for this study. For cases, we obtained ER and PR status (classified as positive, borderline, negative, or unknown) as well as stage and grade of disease, from pathologists, records and personal interviews conducted.

Inclusion and exclusion criteria

All cases of second primary breast cancers were excluded. We stratified our analyses by hormone receptor status, specifically assessing separately the rates of ER+, ER–, PR-positive (PR+), PR–, ER+/PR+, ER+/PR–, ER–/PR+, and ER–/PR– tumors. Women who had an ER and/or PR status that was classified as borderline or was not assessed were excluded from these analyses.

Measuring quality of life (QOL) in breast cancer patients has been the focus of clinical practice and research in recent decades and is of importance in assessing treatment outcomes. This is partly due to the increasing number of breast cancer patients. A. Montazeri et al., (2008) (Fuqua et al., 1993) have studied the QOL in breast cancer patients in a 18 month follow up study period and this work has inspired us to take up such a study. Subsequently we have recorded QOL in patients after and during therapy regimens, using a simple questionnaire.

Histopathological findings

Pathologists measured the tumor sizes in the surgical specimens before preparing histological sections. Measurement of locally advanced carcinoma tumor size was by imaging techniques (mammography and ultrasound before chemotherapy). The pathologist subsequently classified tumors into three groups according to size. Specimens were also classified according to histological grade into grade I (well differentiated), grade II (moderately differentiated), or grade III (poorly differentiated). Staging before random assignment included normal chest x-ray, mammogram, and blood analysis for hematologic, hepatic, and renal function.

Determining the ER/PR status of the tumors

After stratification, the hormone receptor status (ER+/PR+, ER+PR-, ER-/PR+, ER-PR-) was determined. Standard procedures (immuno-histochemical) routinely used in the pathology laboratory determined and scored the estrogen and progesterone receptors.

Adjuvant therapy regimens

The therapies administered to these patients after surgery included a combination of chemo- drugs or hormone (Tamoxifen) therapy or a combination of hormone plus chemo drugs; the combination regimens were as follows:

- FAC (Cyclophosphamide, Adriamycin, 5-FU)
- CMF (Cyclophosphamide, Methotrexate, 5-FU),
- CAF (Cyclophosphamide, Alurubicin, 5-FU) and
- Tamoxifen (hormone therapy)

Statistical analysis

All results were evaluated statistically and presented as tables and figures.

Results

Characteristics of the study group

79-breast cancer patients (IDC) referred to the Hospitals, from

June 2008 to June 2009 formed our study group. Median age at diagnosis was 56 (26-76). Patient and tumor characteristics are summarized in Table 1. There was no familial history of breast cancer among these patients and two-thirds of the patients were postmenopausal.

Tumor size measured in the surgical specimens by the pathologist. The pathologic characteristics of the tumors have prognostic significance. Certain subtypes such as tubular, mucinous, and medullary have a more favorable prognosis than unspecified breast cancer. In an attempt to improve interobserver variability, multiple grading systems have been proposed, with the most widely accepted being the Scarff-Bloom-Richardson (SBR) classification (Le Doussal et al., 2006).

Histological grading of the tumors in pre and post menopausal patients

Results of the classification of tumor grades are presented in Table 1, maximum number of cases were (43%) postmenopausal women with grade-II tumors. There was no significant difference between in the occurrence of the right or the left breast tumors. It was not easy to tell which side is more prone to tumorigenesis (Table 1).

Characterization of the receptor status of the cancer cases

The results of immunohistochemical localization of ER/PR statuses are presented in Figure 1, Table 1. The overall percentage receptor status of the patients showed that estrogen and progesterone receptors (ER+ and PR-) were highest in postmenopausal patients in the study group. Further analysis of the details showed ER- /PR- tumors, were next highest (Table 1, Figure 2).

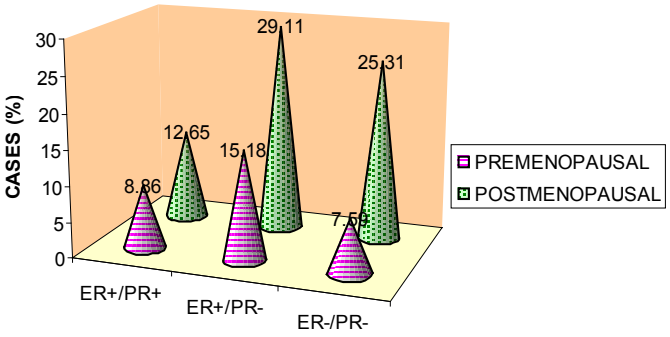
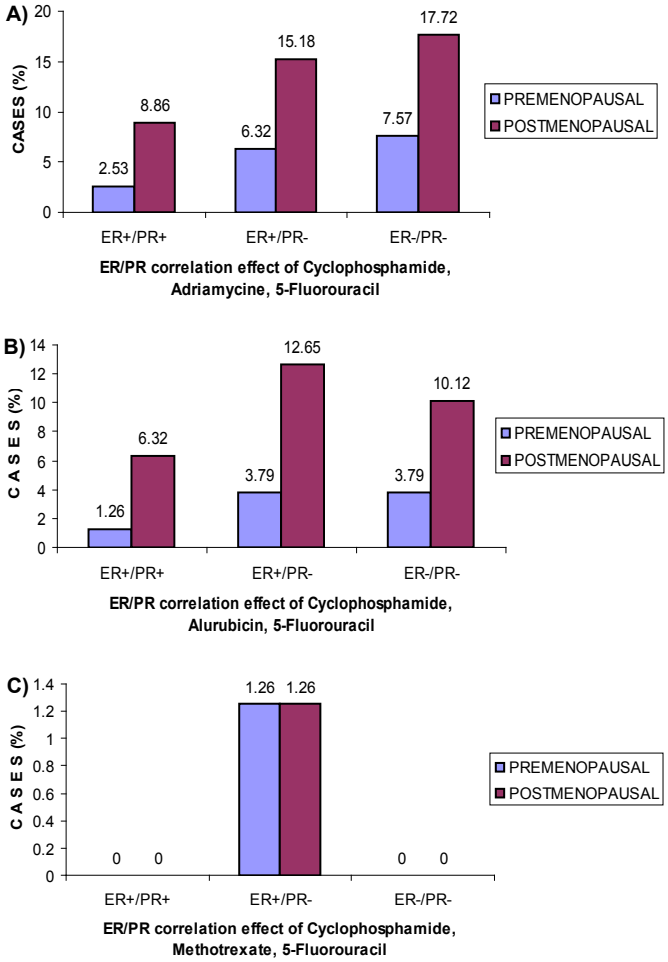


Figure 1: Graphical representation of ER/PR status of 79 Pre & Postmenopausal Breast cancer Patients in the period between 2005-2006.

Tumor Characteristics	Pre menopausal	Postmenopausal
Age	25(35.44%)	54(64.55%)
Tumor size		
<2	02(2.53%)	08(10.12%)
2-5	19(24.05%)	47(59.49%)
>5	00(00.00%)	03(3.79%)
Axillary Nodes		
<3	10(12.65%)	30(37.97%)
4-9	5(6.34%)	14(17.72%)
>10	4(5.06%)	14(17.72%)
Histological Grade		
I	1(1.26%)	2(2.53%)
II	7(8.86%)	34(43.03%)
III	11(13.92%)	17(21.51%)
Right Breast Carcinoma	15(18.98%)	24(30.37%)
Left Breast Carcinoma	12(15.18%)	28(35.44%)
ER/PR Status		
ER+/PR+	7(8.86%)	10((12.65%)
ER+/PR-	12(15.18%)	23(29.11%)
ER-/PR-	6(7.59%)	20(25.31%)

Table 1: Clinical and biological characteristics in pre and postmenopausal Women with Breast carcinoma.



Figures 2: A, B, & C Correlation of ER/PR (Subtypes) status and Different Combinations of Anticancer Drugs in Pre & Postmenopausal Women in Breast Cancer. A: ER/PR correlation, effect of CAF. **B:** ER/PR correlation, effect of FAC. **C:** ER/PR correlation, effect of CMF.

Clinical characterization of the tumor and status of ER/PR

The clinical and biologic tumor characteristics are summarized in Table 2. Overall, in women more than 45 years of age, ER + /PR - and ER- and PR- tumors were found more frequently than ER + /PR + tumors. It was also observed that ER + /PR - tumors were larger in size (greater than 2 cm in diameter) than ER + /PR + tumors (51% versus 45%, respectively; $P < .001$). In addition, 21.51% and 17.72% of patients whose tumors were ER + /PR - and ER-/PR- had four or more axillary nodes involved with tumor compared to patients with 7.59% ER + /PR + tumors (Table 2) .

Adjuvant chemotherapy for all cases

All patients were administered adjuvant systemic chemotherapy, out of 79 cases 13.92% (11 cases) premenopausal and 18.98% (15 cases) postmenopausal cases received FAC combination. 18.98% (15) premenopausal and 36.70% (29) postmenopausal cases received CAF combination. Only 1.26% (1case) premenopausal and 2.53% (2 cases) postmenopausal cases re-

Status	4 or more axillary nodes
ER+PR+	06(7.59%)
ER+PR-	17(21.51%)
ER-PR-	14(17.72%)

Table 2: Correlation between ER and PR Status and Axillary Nodal status (above 4 nodes) of all 79 cases above 45 years of age.

Tumor characteristics	FAC	CAF	CMF
Age			
Pre menopausal	11(13.92%)	15(18.98%)	01(01.26%)
Post menopausal	29(36.70%)	29(36.70%)	02(02.53%)
ER+PR+			
Pre menopausal	03(02.53%)	01(01.26%)	00(0.00%)
Post menopausal	07(08.86%)	05(06.32%)	00(0.00%)
ER+PR-			
Pre menopausal	05(06.32%)	03(03.79%)	01(01.26%)
Post menopausal	12(15.18%)	10(12.65%)	01(01.26%)
ER-PR-			
Pre menopausal	06(07.57%)	03(03.79%)	00(0.00%)
Post menopausal	14(17.72%)	08(10.12%)	00(0.00%)

FAC- Cyclophosphamide, Adriamycine, 5-Fluorouracil
CAF- Cyclophosphamide, Alurubicin, 5-Fluorouracil
CMF- Cyclophosphamide, Methotrexate, 5-Fluorouracil

Table 3: Correlation of ER/PR (Subtypes) status and different combinations of anticancer drugs received by pre & postmenopausal cases.

Characteristics	Tamoxifen Users (n=40)
Postmenopausal	37
Premenopausal	3
Estrogen Status	
ER Positive	36
ER Negative	4
Duration of Tamoxifen-20mg	
Up to 1 year	16
>1-2 years	6
>2-3 years	2
>3-4 years	0
>4-5 years	2
above 5years	1(12 years)
Side Effects	
Hypertension	9

Table 4: Clinical and Pathological Information of Tamoxifen receiving patients.

ceived CMF combination. Drugs in relation to ER/PR status of these patients are presented in Table 3.

Hormonal therapy (Tamoxifen) for selected patients

In this study, 40 cases were given Hormonal therapy (Tamoxifen). Among these only 7.5% (3) were premenopausal. The other 92.5% (37) cases were postmenopausal, and in this group 90% (36) cases were ER+PR+ and 2.5% (1) case was ER+PR-. Most of the hormonal therapy cases showed good response. We recorded the time duration of tamoxifen receiving cases. Out of 40 cases 40% (16 cases) were using Tamoxifen for the last one year during the study period, 15% (6) cases were between 1-2 years , 5% (2) cases were between 2-3 years, 5% (2) cases were between 4-5 years , and only 2.5% (one) case was using from last 12 years. This also corresponded to the QOL of the surviving patients. All the cases showed good response, but 22.5% (9) cases were suffering from hypertension (Table 4).

Response rates to different combinations of chemotherapy

Response rate in these patients was categorized as: a) satisfactory, b) poor and c) good. The results are presented in Table 5.

Discussion

Breast cancer cells that are ER+ depend on estrogen to grow, hence anti-estrogen hormonal therapy administered blocks the receptors or to reduce the amount of estrogen that can get to the receptors, so that the cancer cells may shrink or die. Our results showed that several post-menopausal women were ER+. As mentioned earlier hormone therapy was the initial treatment for metastatic breast cancer with ER/ PR positive tumors. Thus, tamoxifen- a non-steroidal anti-estrogen drug was the first choice for the patients who developed metastatic disease. More recently, two modern aromatase inhibitors like Anastrozol and Letrozol are used. These agents were more effective in postmenopausal women and are less toxic. Patients who did not respond to initial hormonal therapy were receiving chemotherapy mostly to cater for their QOL.

Updates on the recent developments in this area show that the adrenal glands produce another hormone, which converts into estrogen, by the body. This estrogen can stimulate the tumor growth, and the women show ER+ status (even after menopause). Another exciting new hypothesis is that a new ER coded by a different gene identified. This ER is termed ERb, and expressed in normal breast and tumor tissue and reported to be up- regulated after 48 hours of estrogen treatment. Hence, the ER-b may help predict the tumor response to anti estrogen therapy.

Another hypothesis, which researchers have suggested, is that two enzymes like acetylase and deacetylase, alternately add or remove acetyl group at the receptor and thus affect the estrogen receptors and the hormone-binding proteins that bind to estrogens inside cells. However it is not yet clear how the modification of natural receptors and how an addition of acetyl group regulates the activity of receptors in response to estrogens. Our Database searches have provided us useful information for locating breast cancer genes spread over the chromosomal spectrum and their functional aspects (Shanker et al., 2007; Khan and Jamil, 2008). This information has been of additional benefit in understanding the data of the multiple locations of the breast cancer genes.

Since breast carcinoma is a steroid hormone–dependent tumor it is obvious that sex steroid hormones, especially estrogen, play an important role in the development of breast cancer. Early menarche, late menopause, benign breast disease and hormone replacement therapy have been shown to be associated with increased risk for breast cancer (Trentham-Dietz et al., 1998). However, the role of progesterone in breast cancer development is still resistance factor. One hypothesis proposed to explain the parity effect is that hormonal stimulation by estrogen and progesterone induce a differential switch in a specific stem cell population that results in changes in the intracellular pathway governing proliferation and response to carcinogens. Hormone receptor status is one of the most important prognostic factors affecting the QOL for breast cancer patients. An increase in hormone receptor expression is associated with inhibition of cell proliferation and subsequently weakens tumorigenesis. ER+ tumors show a lower incidence of recurrence and a longer disease-free

S. No	Drug combinations	Patients	Response rate	No. of Individuals (%)
	Cyclophosphamide Adriamycin 5-FU [FAC] N=47	Pre menopausal	Satisfactory	5(10.63%)
			Good	3(6-38%)
			Poor	12(25.53%)
		Post menopausal		
			Satisfactory	17(36.17%)
			Good	4(8.51%)
			Poor	6(12.76%)
2	Cyclophosphamide Alrubicin 5-FU [CAF] N=29	Pre menopausal	Satisfactory	5(17.24%)
			Good	2(6.89%)
			Poor	2(6.89%)
		Post menopausal		
			Satisfactory	9(31.03%)
			Good	6(20.69%)
			Poor	5(17.24%)
3	Cyclophosphamide Methotrexate 5-FU [CMF] N=3	Pre menopausal	Satisfactory	3(100%)
		Post menopausal		(Nil)

Table 5: Therapy-Response of breast cancer women receiving different combination of drugs.

interval, regardless of tumor size or lymph node status (Suzuki et al., 2005). However, the prognostic value of PR status is controversial. It is important to take the PR status be taken into account with ER status because patients with both ER+ and PR+ tumors usually have a better prognosis than patients with ER+ and PR- tumors.

When we compared the receptor status between pre and postmenopausal women, out of total 79 cases we found that 35.44% (25cases) were premenopausal and 64.55% (54 cases) were postmenopausal. We also found that 8.86% (7cases) in premenopausal and 12.65% (10cases) in postmenopausal were ER+/PR+ status. 15.18% (12 cases) in premenopausal and 29.11% (23cases) in postmenopausal were ER+/PR- status. However we did not observe any cases in premenopausal women and only 1.26% (one case) in postmenopausal with ER-/PR+ status, and 7.59% (6 cases) in premenopausal and 25.31% (20 cases) in postmenopausal were ER-/PR- status (Table 1).

Demographic and clinical features at presentation

The clinical and biologic tumor characteristics are summarized in Table 1. Overall, in women more than 45 years of age, ER + /PR - and ER- and PR- tumors were found more frequently than ER + /PR + tumors (82% versus 77% respectively; $P < .001$). However, ER + /PR - tumors were larger (greater than 2 cm in diameter) than ER + /PR + tumors (51% versus 45%, respectively. In addition, 21.51% and 17.72% of patients whose tumors were ER + /PR - and ER-/PR- had four or more axillary nodes involved with tumors compared to patients with 7.59% ER + /PR + tumors.

Previous studies reported that risk of ER+PR+ breast cancer is positively associated with nulliparity, a later age at first birth, a later age at menarche, and a higher body mass index (BMI; weight in kg/height in m2), but these factors were inversely related to the risk of ER–PR– tumors (Taucher et al., 2003; Giuffrida et al., 1992). These observations suggest that tumors subclassified by joint steroid receptor status may actually represent distinct forms of breast cancer with differing etiologies. Family history of breast or ovarian cancer nor medical radiation exposure to the chest did not relate to ER+PR+ tumors, yet both factors increased ER–PR– tumor risk. As age increased, the proportion of women with ER+PR+ tumors increased, and this finding corresponded primarily with a decline in the proportion of women diagnosed as having ER–PR– tumors. Recent data indicate that ER+PR- disease is characterized by a lower response rate to estrogen deprivation, has a worse prognosis compared to ER+ PR+ disease, and may be dependent on other signaling pathways.

More features that are aggressive were the characteristics of ER+/PR- tumors, common in older patients, compared to ER+/PR+ tumors. Incidence rates for ER+/PR+ and ER-PR- breast cancer differed by age and menopausal status. The influence of parity and past use of postmenopausal hormones differed between the two tumor types. Metastatic and adjuvant treatment determined that tamoxifen is less efficacious in ER + /PR- tumors than in ER + /PR + tumors.

In this investigation, the cases were categorized into premenopausal and postmenopausal groups, 45 years of age being arbitrarily taken as the outer limit for premenopausal group. The choice of this was to reflect the fact that most women who were menstruating were < 45 years, whereas those > 45 years had either irregular / infrequent cycles or no menstruation. Out of 79 cases, overall 34.44% were premenopausal and 64.55% were postmenopausal. Further sub-classification of the cases was based on estrogen receptor status such as 15.18% cancers were premenopausal and 29.11% postmenopausal with ER+ / PR-ve, whereas 7.59% cases were premenopausal and 25.31% postmenopausal with ER-/ PR-ve, and 8.86% cases were premenopausal and 12.65% postmenopausal with ER+/ PR +ve statuses. The frequencies of ER+/ PR- and ER-/PR- receptors were higher in postmenopausal women. One possible explanation for this could be due to the levels of circulating estrogen and progesterone, occurring in this group at that time which influences the QOL of the patients suffering from breast cancer.

ER/PR status and overall survival period

Women with tumors that are ER+PR+ have longer disease-free and overall survival compared to those identified with ER-PR negative cancers, while women with ER+PR- tumors show

intermediate survival (McGuire et al., 1991). Although it has been concluded that ER+PR+ ("hormonally responsive") tumors and ER-PR negative tumors("hormonally unresponsive") represent two distinct tumor-types from a biological and clinical perspective (Thorpe et al., 1987). Tumors discordant for ER and PR status may represent additional profiles (Fuqua et al., 1993). Clinical data have shown that ER-PR- and ER+PR+ tumors differ from each other in their natural history, their response to therapy, and their biological characteristics. In contrast, limited current evidence suggests that women with ER-PR+ tumors appear to fit a profile which strongly resembles ER+PR+ tumors, and that these tumors may represent a subset of ER+PR+ tumors or be false negative for ER status (Fisher et al., 1980). A mutant ER may characterize some tumors with constitutive transcriptional activity (Montazeri et al., 2008). However, several aspects of this hormonal therapy are still puzzling, since there are a large number of ER+ breast cancer patients who do not respond to anti-estrogens. In addition, there are patients who initially respond to anti-estrogen therapies eventually acquire anti-estrogen resistance despite retention of ER in many tumor cells. Besides, there are some reports of ER negative patients who benefit from anti-estrogen treatments. These hormonal statuses also influence the survivability and QOL of patients.

Hormonal status and response to therapy

Steroid hormone receptors have proven to be the most important predictive markers for selection of systemic treatment. This was clear in the selection of postoperative neoadjuvant chemotherapy, and endocrine treatment for premenopausal as well as postmenopausal patients (Enger et al., 2000). Assessment of systemic treatment were with respect to menopausal and receptor statuses. The premenopausal group (35%) and postmenopausal group (65%) received systemic chemotherapy. When systemic therapy was correlated to receptor status, it was observed that the status of the receptor had a significant impact on treatment choice for both premenopausal and postmenopausal patients. Chemotherapeutic agents were active in breast cancer when given in combination regimens often administered are FAC (Cyclophosphamide, Adriamycine, 5-FU) CMF (Cyclophosphamide, Methotrexate, 5-FU), CAF (Cyclophosphamide, Alurubicin, 5-FU). Our in-vitro studies on drug combinations determined the toxic effects of single versus combined effects of neoplastic drugs (Suman and Jamil, 2006). Another study suggests that Herceptin may be beneficial regardless of the ER/PR status 59.49% cases received FAC combination, and in this group 27.8% were satisfactory (6.3% premenopausal, and 21.5% postmenopausal). 8.8% showed good response (3.7% premenopausal, and 5% postmenopausal), and 22.78% cases showed poor response (15.18% premenopausal, and 7.59% postmenopausal). About 32.9% received CAF combination, and in this group 17.72% were satisfactory (6.3% premenopausal, and 11.39% postmenopausal), 8.8% cases showed good response (1.26% premenopausal, and 7.59% postmenopausal) and 8.8% showed poor response (1.26% premenopausal, and 7.59% postmenopausal). About 3.7% cases which received CMF combination, showed satisfactory response and all cases were premenopausal (Table 5).

QOL observations

Studies on QOL, have shown decreased health-related quality of life because of chemotherapy side effects, may predict early treatment discontinuation in patients On the other hand, some studies on post-treatment adjustment of breast cancer survivors have shown that breast cancer patients might enjoy from a good quality of life. In one study, patients reported poor social functioning following completion of breast cancer treatment. Similarly, studies have found that breast cancer survivors suffer from poor social functioning (Schou et al., 2005; Wefel et al., 2004).

Whether or not receptor status plays an important role as a predictive marker for response to chemotherapy is still an open question. In metastatic breast cancer, Lippman and Allegra, (1980) argued that patients with ER-negative tumors show a much better response rate than those with ER-positive tumors, although other authors did not confirm this data. In the adjuvant situation, chemotherapy appears more beneficial in receptor-negative patients. Furthermore, most of the functional scores did not improve over time and this is in contradiction to the findings from some existing literature (Engle et al., 2003; Engle et al., 2004).

Conclusion

Overall, we found that in postmenopausal women ER^+/PR^- and ER^-/PR^- tumors were more frequent than ER^+/PR^+ tumors. However, ER^+/PR^- tumors were larger than ER^+/PR^+ tumors. A recent study by Grann and coworkers (Grann et al., 2005) also suggested that the higher risks of mortality was in women with ER+/PR-, ER-/PR+, and ER-/PR- tumors, compared to women with ER+/PR+ tumors. Because hormone receptor status is known to vary by both stage and race, we also stratified this analysis by stage and by nodal status race. The results obtained in this study showed that there were wide ranges of therapy approaches employed by Oncologists in breast cancer therapy (purely the decision of the medical oncologist attending on the patient). The determinant factors correlated with menopausal status, patient's age and, were lower than expected to receptor status. Although hormonal therapy was of comparable efficacy to chemotherapy, but chemotherapy was associated with higher toxicity and lower quality of life (QOL). Engle et al (Engle et al., 2004) reported that their study also showed that overall breast cancer patients perceived benefit from their adjuvant treatment. However, sustained problems such as fatigue, pain, sleep disturbances and arm symptoms were prevalent which were very much similar to our findings. Indeed, management of these by targeted interventional programs is required. In addition, impaired body image, decreased sexual functioning and sexual enjoyment in patients, must be seriously considered in long-term survivors of breast cancer, to improve their overall quality of life. Chemotherapy seems to be preferred more frequently than hormonal therapy for receptor positive metastatic breast cancer. Although data on tumor characteristics may add information regarding treatment; the traditional pathological and morphological examination may be linked to the clinical behavior of tumors, but hormonal status is clearly important as predictive and prognostic factor for therapy. However, this study was limited due to its small cohort of breast cancer patients also there was a drop-out-rate of nearly one third of patients during the follow-up courses.

Acknowledgement

We are thankful to all the participants of this study, even though it is a retrospective study. We are also thankful to the Patholo-

gists and Consulting Oncologists from various Hospitals, our special thanks to Dr. Nori Dattatreyudu, Dr. Ch. M. Vamsy, Dr. S. Murthy and Dr. Susheela for their valuable inputs and advise in preparing this manuscript. We are immensely thankful to the Director of NIN (Dr. B. Sesikeran) who has helped us to analyse and project this data in a systematic way. We are thankful to the management of Mahavir Hospital & Research Centre for the facilities provided.

Conflict of Interest

The authors declare that they have no conflict of interest.

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