ISSN NO. 2320-5407

Journal homepage:http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Triple negative breast cancer (TNBC), the surgeons and physicians dilemmain Pakistan.

Umair-ul-Islam[1], Afsheen Arif[2], SitwatZehra[3], RafiqKhanani[4], AbidAzhar[5]

1. Department of Surgery, Dow Medical College and Civil Hospital, Associate Professor, Dow University of Health Sciences, Karachi, Pakistan.
2. Medical Biotechnology, The Karachi Institute of Biotechnology and Genetic Engineering (KIBGE), Assistant Professor, University of Karachi, Karachi Pakistan
3. Medical Biotechnology, The Karachi Institute of Biotechnology and Genetic Engineering (KIBGE), Assistant Professor, University of Karachi. Karachi Pakistan.
4. Department of Pathology, Dow International Medical College, Professor, Dow University of Health Sciences, Karachi Pakistan.
5. Dean, Faculty of Science and Meritorious Professor, Director General, The Karachi Institute of Biotechnology and Genetic Engineering (KIBGE), University of Karachi, Karachi Pakistan

Manuscript Info

Manuscript History:

Received: 29 November 2014
Final Accepted: 22 December 2014
Published Online: January 2015

Key words:

Triple negative breast cancer, estrogen, progesterone, her 2/neu, Karachi, Pakistan, ethnic.

Corresponding Author

Afsheen Arif

Abstract

Purpose:

Breast cancer is one of the most common feminine cancers globally. It accounts for about 15-20% and among these TNBC accounts for 15% of all breast cancer patients. This is the most aggressive form of breast cancer. Breast cancer is a diversified group of biological cancers. Its subtypes have its own history, histopathology, hormone receptors and hormone epidermal growth factor receptor 2 (Her 2). The incidence rates of breast cancer and oral cancer in Karachi are highest in Asia. This study aims to provide data about molecular subtypes of breast cancer in Pakistan.

Methods:

A cross sectional multi Centre study conducted in surgical departments of CHK, ASH, JPMC, LNH, Institute of Surgery and Medicine (ISM) and other hospitals, after the approval of ethical review committee. A total of 160 patients were recruited from 2010- 2013. Descriptive analysis contains age, ethnicity, BMI, marital status and religion of the cohort. Reproductive risk factors were also taken under consideration like first menstrual age, pregnancies, no. of children, breast feeding and duration, first delivery age, last delivery age, menopause status and hormonal or birth control medications, other life style risk factors like medical allegories, smoking, alcohol consumptions, soft drink intake were also assessed. Diagnosis was done by physical examination, mammography, immunohistochemistry, Fine needle aspiration cytology and FISH analysis. Molecular classification was done according to ASCO/CAP, 2013 guidelines. Statistical data analysis was done by SPSS 17.0.

Results:

The total frequency for TNBC is 34.3%. The mean age is 45.69±13.9 and BMI is 24.52 ± 4.95. Urdu speaking and Punjabis are most effected ethnic groups. The type of each patient is categories as ILC 6.55%, Mucinous 2.45%, Invasive adenocarcinoma 0.81%, metaplastic 4.09%, and IDC 86%. Position of tumor left (48%) and right (52%). Consistency is hard and firm mostly margins are well defined. Tumor size ranges 2-5cm (65.5%) and ≥ 5cm (34.5%). The largest size of tumor was 15cm X 10cm.Tumor site were centrally placed (7.3%), lower inner quadrant (5.5%), lower outer quadrant

(25.5%), lower outer inner quadrant (1.8%) upper inner quadrant (5.5%), upper outer quadrant (32.7%) and upper outer inner quadrant (9.1%). upper outer lower quadrant (10.9%).

Conclusions:
Triple negative breast cancer is 15-20% reported globally, however current study found 34.3%. Ladies from Punjabi origin are more prone to TNBC. Current research had found that adding the chemotherapy drug carboplatin or the angiogenesis inhibitor Avastin to standard chemotherapy drugs could produce a rapid decline in TNBC, would help clinicians to treat breast cancer patients on the basis of their molecular profile.

INTRODUCTION

There are four molecular subtypes, luminal A, luminal B, Her 2 positive cancer and triple negative breast cancer (TNBC) (Laurentiisa, 2010). TNBC was first described by Wetzels et al (1989). They are so called basal type because the gene expression of these cancers have similar pattern to the cells in the deeper basal layer of breast ducts and glands. TNBC is characterized by lack of expression of estrogen receptor (ER) and progesterone receptor (PgR), and the absence of HER2 protein overexpression by routine clinical assays for these biomarkers. TNBC lack the therapeutic targets in comparison to other breast cancer types and had worst prognosis, being challenge for the clinicians (Chen and Russo, 2009).
TNBC are more prevalent in African-American women (Dawson, 2009). This subtype predominantly occurs in women of African origin about 26% having large tumor size. It is estimated that out of 1 million breast cases diagnosed in the world in 2008, they represented 172,695. The study carried out in different population reveals that this cancer is about 15-20% (Irvin, 2008). Incidences of breast cancer in Karachi are highest among Asian population and it accounts for one third of all, 2018 cancers registered with a standardized age ratio 51.7 in Karachi Cancer Registry (Bhurgri, 2000).
These cancers are high grade cancers elevated mitotic count scant stromal content and lymphocytic response and apoptotic cells. Histologically, they are largely ductal in nature but several unusual histologic samples are also overrepresented like metaplastic, atypical or typical medullary, adenoid cystic carcinoma (Livasy, 2006, Reis-Filho, 2006, Beatty, 2006, Jacquemier, 2005, Cleator, 2007). Lymph nodes are generally not involved as shown by Caroline breast cancer study (Carey, 2006). Clinically they tend to occur in younger age group especially those who had BRCA1 mutation or those have high mutation rate of p53 genes, which is explanatory for its aggressive behavior (Eroles, 2012). BMI increases tumor size among premenopausal women (Yang, 2007). Hormone therapy and anti Her2 therapy are ineffective. They grow quickly and there outcome is very poor, however to some extent chemotherapy is beneficial. It is noteworthy that the relapse rate is aggressive and generally lung, central nervous system and lymph nodes are involved (Kennecke, 2010, Smid, 2008).

1. Materials and Methods:

The study is a cross sectional study and sampling was done Nov' 2010 till March' 2013. All breast cancer patients were included in the study. Patients undergoing surgical procedure for carcinoma breast were informed and asked for consent to participate in this study. Patients were explained in their language about the study, they were also informed that if they give consent for this study, histopathology, immunohistochemistry and FISH analysis will be performed free of cost for them. Hepatitis B, C positive patients, pregnant, terminal and non-operable patients were excluded from the study.
The descriptive analysis includes age, gender, BMI, ethnic groups, marital status and religion of the patients. Life style risk factors include family history, smoking, tea and coffee intake, alcohol consumptions and medical allergies. The factors of reproductive life like first menstrual cycle, pregnancies, no. of children, breast feeding conditions, age

at first and last delivery, menopause, hormonal therapy and birth control strategies were also taken into consideration(Dolle,2009).
Clinical parameters include type of cancer, pathological stage, clinical stage, tumor size, grading, axillary node involvement, position, shape, site, fixitivity, margin, nipple condition and discharges, consistency,Her-2neu status, ER, PgR status.

2. Results:

Triple negative breast cancer was the most prevalent group of the study 55 (34.3%). The mean age of this subtype is 45.69±13.9. Interestingly most patients are young in this subclass age range 28-50, i.e. (37) 67.3%. Urdu, Punjabi, Sindhi and Pashto are common ethnic groups in this subclass (22) 40%, (12) 21.8%, (10) 18.2% and (5) 9.1% respectively.
In TNBC subtype (44) 80% were invasive ductal carcinoma, metaplastic ductal cancer (3) 5.5%, each case of focal invasive ductal cancer, IDC with B cell lymphoma, invasive mucinous carcinoma and medullary carcinoma are observed. The most prevalent clinical stage is II (Table 1). In pathological staging T2,N0,Mx (16) 29.1% is more common followed by T2,N1,Mx (10) 18.2% T3,N0,Mx (6) 10.9% and T3,N1,Mx (5) 9.1%. These are high grade cancers hence 56.4% patients are Grade III and 34.5% are of Grade II.
Estrogens receptors are negative 100%. PgR are 100% are negative. Her2neu is 0 for 58.2%, 1 for 36.4% and 2+ for 3.6%, which are FISH negative. Lymph nodes involvement are 69.1% are negative and 29.1% are positive, palpable, mobile, ipsilateral and one case for palpable, fixed ipsilateral was observed. Tumor size are 64.5% of 2-5cm and 34.5% are <5cm. In this study 17.7% of the patients have the slit or inverted nipple, secondary to the underlying tumor and bloody discharge from the nipple was only 2.5% which is quite less than previously mention study (Afridi, 2012). Mastectomy was done and T1 level of lymph nodes were dissected out of patients.

3. Tables:

Clinical Stage			
	Frequency	Percent	Cumulative Percent
I	1	1.8	1.8
II A	20	36.4	38.2
II B	12	21.8	60.0
III A	2	3.6	63.6
III B	13	23.6	87.3
IV	7	12.7	100.0
Total	55	100.0	

Table 1: Frequency distribution of clinical stage in triple negative subtype patients

Grading			
	Frequency	Percent	Cumulative Percent
I	1	1.8	1.8
II	19	34.5	36.4
III	31	56.4	92.7
NA	4	7.3	100.0
Total	55	100.0	

Table 2: Frequency distribution of tumor stage in in triple negative subtype patients

4. Discussions:

Molecular analysis of hormonal (ER and PgR) and Her2 receptors in this study showed that number of TNBC are most common. It accounts for 34.3% of all the breast cancer in this study. It is the highest percentage seen in

comparison to other studies (Swede, 2011, Carey,2006, Yang, 2007)where on an average it is 15-20% only in Caroline breast cancer studies; the premenopausal African American women had up to 27% of basal cell cancer. The patients are of younger age group 45.6 years (Vallejos, 2010) compared to other studies where the age is beyond late 50s' (Swede, 2011, Yang, 2007, Vallejos, 2010). The tumor size of greater than 5cm is 34.5% and between 2-5cm is 65.5%, no tumor is seen below 2 cm in the study. This is accordance with all the large studies. The lymph node status is less positive than negative (29.1% vs 69.1%) and this is also shown in all the studies globally. Histologically 80% of the tumors are invasive ductal carcinoma, which is in accordance with the global literature except with Spitale (2010), but the second common tumor seen in this study is metaplastic ductal carcinoma, which is in contrast to other studies where mixed and other breast cancers are second in number (Onitilo, 2009 and Yang, 2007)

ER and PgR are highly significant for the treatment in breast cancer on individual basis, due to highly sensitive to chemotherapy and hormonal therapy. Her 2 positive tumors again respond well to monoclonal antibodies (Herceptin) but ER/PgR and Her 2 negative tumors (TNBC) do not respond commonly used chemotherapy. Recently some studies have shown that anthracyclin have some beneficial effects on these tumors, but these tumors being aggressively they metastasized very early and relapse free interval is less than five years. Surprising in this study span over four years and despite the fact given non-anthracyclin chemotherapy the patient of stage II and III have followed up of for two and no death have been reported only seven enter into stage IV. All these patients subjected to CMF(cyclophosphamide, methotrexate and fluorouracil) six cycles. Majority of the patients have no family history.

It is interesting to note that all these tumors were solid whereas reports mention that they can be cystic and ill-defined, this could be easily determined by ultrasound (Kandil, 2012). In other studies mostly patients were reported with stage I,conversely in this study patients are with stage II and III due to neglecting health issues of females and misguidance of consultants. Patient with Stage II were 58.2% whereas other studies reports more patients lies in Stage I (Kandil, 2012, Montagna, 2013). Histologically none of our patients represents tumor necrosis, whereas it is 62-66% in other studies (Elsawaf, 2013). Lymph node conditions are in concordance to the studies.

It has been reported that risk factors like age, pregnancy history, post menopause hormonal use, family history for breast cancer and BMI after menopause has a significant effect on both receptors. In our population such risk factors like alcohol eliminated due to society constrains, however other potential risk factors like breast feeding and fertility has no effect on the disease status.

TNBC have contradictory statements about lymph nodes involvement, the Caroline breast cancer study suggested no involvement however other school of thought showed positive lymph nodes involvement (Telli,2010 and Dawson, 2009). In our data it is found that 29% patients are with positive lymph nodes, which is in accordance with Vallejos et al and Spitalel et al.

TNBC is a subtype of breast cancer with challenging biological features. It has no known specific target so far and is usually considered an aggressive treatment-resistant disease. TNBC accounts 15% globally and it is present in our population at a higher rate 34.3%. The rate of occurrence of breast cancer is lower in our population but death rate is higher may be due to increase number of TNBC patients. The genetic makeup and environmental factors that interplay are needed to explore (Dolle, 2009).

5. References:

- Afridi SP, Ahmed S (2012) Profile of Breast Cancer patients Journal of surgery Pakistan 17: 116-120.
- Beatty JD, Atwood M, Tickman R, Reiner M (2006) Metaplastic breast cancer: clinical significance. Am J Surg 191:657–664.
- Bhurgri Y, Bhurgri A, Hassan SH, Zaidi SH, Rahim A, Sankaranarayanan R, Parkin DM (2000) Cancer incidence in Karachi, Pakistan: first results from Karachi Cancer Registry. Int J Cancer 85:325-329.
- Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, et al (2006) Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295:2492–2502.
- Chen JQ and Russo J (2009) ERα-negative and triple negative breast cancer: Molecular features and potential therapeutic approaches BiochimicaetBiophysicaActa 1796:162–175.
- Cleator S, Heller W, Coombes RC (2007) Triple-negative breast cancer: therapeutic options. Lancet Oncol 8:235–244.
- Dawson SJ, Provenzano E, Caldas C (2009) Triple negative breast cancers: clinical and prognostic implications. Eur J Cancer 45:27–40.

- Dolle JM, Daling JR, White E (2009) Risk Factors for Triple-Negative Breast Cancer in Women Under the Age of 45 Years, Cancer Epidemiol Biomarkers Prev18:1157-1166.
- Dreyer G, Vandorpe T, Smeets A, Forceville K, Brouwers B, Neven P, Janssens H, Deraedt K, Moerman BP, Calster BV, Christiaens MR, Paridaens R, Wildiers H (2013) Triple negative breast cancer: Clinical characteristics in the different histological subtypes, The Breast 22: 761e766.
- Elsawaf Z, Sinn HP, Rom J, Bemejo JL (2013) Biological subtypes of triple-negative breast cancer are associated with distinct morphological changes and clinical behaviour. The Breast22:986-992.
- Eroles P, Bosch A, Pérez-FidalgoJA,Lluch A (2012) Molecular biology in breast cancer: Intrinsic subtypes and signaling pathways. Cancer Treatment Reviews 38: 698–707.
- Irvin WJ, Carey LA (2008) What is triple-negative breast cancer?Eur J Cancer. 44:2799-2805.
- Jacquemier J, Padovani L, Rabayrol L, Lakhani SR, Penault-Llorca F, Denoux Y, Fiche M, Figueiro P, Maisongrosse V, Ledoussal V, et al (2005) Typical medullary breast carcinomas have a basal/myoepithelial phenotype. J Pathol 207:260–268.
- Kandil D, Khan A (2012) Triple negative breast carcinoma: the good, the bad and the ugly. DiagnHistopathol18:210–216.
- Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, Nielsen TO, Karen Gelmon(2010) Metastatic behavior of breast cancer subtypes. J ClinOncol 28:3271–3277.
- Laurentiisa MD, Cianniellob D, Caputob R, Stanzioneb B, Arpinob G, Cinieric,d S, Lorussoe V, Placidob SD (2010) Treatment of triple negative breast cancer (TNBC): current options and future perspectives, Cancer Treatment Reviews 36S3:S80–S86.
- Livasy CA, Karaca G, Nanda R, Tretiakova MS, Olopade OI, Moore DT, Perou CM (2006) Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol 19:264–271.
- Montagna E, Maisonneuve P, Rotmensz N, Cancello G, Iorfida M, Balduzzi A, Galimberti V, Veronesi P, Luini A, Pruneri G, et al (2013) Heterogeneity of Triple-Negative Breast Cancer: Histologic subtyping to inform the outcome. Clinical Breast Cancer13:31-39.
- Onitilo AA, Engel JM, Greenlee RT, Mukesh BN (2009)Breast cancersubtypesbased on ER/PR and Her2expression: comparison of clinicopathologic features and survival. Clin Med Res 7:4-13.
- Reis-Filho JS, Milanezi F, Steele D, Savage K, Simpson PT, Nesland JM, Pereira EM, Lakhani SR, Schmitt FC (2006) Metaplastic breast carcinomas are basal-like tumours. Histopathology 49:10–21.
- Smid M, Wang Y, Zhang Y, Sieuwerts AM, Yu J, Klijn JG, Foekens JA, Martens JW (2008) Subtypes of breast cancer show preferentialsite of relapse. Cancer Res 68:3108–3014.
- Spitale A, Mazzola P, Soldini D, Mazzucchelli L, Bordoni A (2009) Breast cancer classification according to immunohistochemical markers: clinicopathologic features and short-term survival analysis in a population-based study from the South of Switzerland. Ann Oncol20:628-635.
- Swede H, Gregorio DI, Tannenbaum SH, Brockmeyer JA, Ambrosone C, Wilson LL, Pesan MA, Gonslaves L, Stevens RG, Runowicz CD (2011) Prevalence and Prognostic role of Triple-Negative Breast cancer by Race: A surveillance Study. Clin Breast Cancer 11:332-341.
- Telli ML, Ford JM (2010) Novel treatment approaches for triple-negative breast cancer. Clin Breast Cancer 10:E16–E22.
- Vallejos CS, Gomez HL, Cruz WR, Pinto JA, Dyer RR, Velarde R, Suazo JF, Neciosup SP, León M, de la Cruz MA et al (2010) Breast Cancer Classification According to Immunohistochemistry Markers: Subtypes and Association With Clinicopathologic Variables in a Peruvian Hospital Database. Clinical Breast Cancer 10:294-300.
- Wetzels RH, Holland R, Haelst UJ, Lane EB, Leigh IM, Ramaekers FC (1989) Detection of basement membrane components and basal cell keratin 14 in noninvasive and invasive carcinomas of the breast. Am J Pathol 134:571–579.
- Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, Hewitt SM, Anderson WF, Szeszenia-Dabrowska N, Bardin-Mikolajczak A et al (2007) Differences in risk factors for breast cancer molecular subtypes in a population based study. Cancer Epidemiol Biomarkers Prev 16:439–443.