Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/17815
DOI URL: http://dx.doi.org/10.21474/IJAR01/17815

RESEARCH ARTICLE

SYNCHRONOUS BILATERAL BREAST CANCER RIGHT HER 2 POSITIVE AND LEFT HER 2 NEGETIVE- A CASE REPORT

Mohammed Junaid Javed[1] and Dr. Sanath K.[2]

1. Pursuing Pharm D (Doctor of Pharmacy) BhaskarPharmacy College, JNTU, Moinabad, Hyderabad, Telengana, India.
2. MBBS, DNB (Medical Oncology) Department of Medical Oncology, Basavatarakam Indo American Cancer Hospital & Research Institute, Hyderabad, Telengana, India.

Manuscript Info

Manuscript History
Received: 05 September 2023
Final Accepted: 09 October 2023
Published: November 2023

Abstract

Bilateral breast cancers (BBCs) represent 2–11% of breast cancers. The diagnosis of breast cancer at the same time or up to 6 months in both breasts is known as Synchronous bilateral breast cancer (s-BBC).[1,2]In about 15% to 20% of breast cancers, the cancer cells make too much of a growth-promoting protein known as HER2. These cancers, known as HER2-positive breast cancers, tend to grow and spread more aggressively than HER2-negative breast cancers. Targeted drug therapy uses medicines that are directed at (target) proteins on breast cancer cells that help them grow, spread, and live longer. Anti-HER2 therapies (also called as HER2 inhibitors or HER2 targeted therapies) are a class of medicines used to treat all stages of HER2-positive breast cancer and certain HER2-low breast cancers.Trastuzumab is currently used sequentially after completion of anthracycline-based chemotherapy as a single agent or in combination with taxanes. In this case report we present a female 51 year old patient with synchronous bilateral breast cancer Left breast wasHER2 negative cT2N0M0, stage I and Right breast was HER2 positive cT2N2M0 stage Ia, both breast cancers were hormone receptor positive. The patient was administered six cycles of Inj. genexol-PM, Inj. carboplatin, Inj. pertuzumab, Inj. trastuzumab, Inj. Pegasta as NAC, Followed by bilateral radical mastectomy, patient showed a complete tumor reduction with residual node in right breast contrary to left breast which showed partial response. (Left breast ypT1N0 (sn)M0 and right breast ypT0N1aM0).

Introduction:-

In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. Breast cancer are epithelial tumors of ductal or lobular origin.Factorsthat increase the risk of breast cancer includes increasing age, obesity, harmful use of alcohol, history of radiation exposure, reproductive history, tobacco use and postmenopausal hormone therapy,Family history increases the risk,inherited high penetrance gene mutations greatly increase breast cancer risk, the most dominant being mutations in the genes BRCA1, BRCA2 and PALB-2.[3]It is the most frequently diagnosed life-threatening cancer in women and the leading cause of

Corresponding Author:- Mohammed Junaid Javed
Address:- Pursuing Pharm D (Doctor of Pharmacy) Bhaskar Pharmacy College, JNTU, Moinabad, Hyderabad, Telengana, India.

cancer death among women. They may be asymptomatic, pain and discomfort are uncommon. Often detected as an abnormality on a mammogram. Evaluation includes clinical examination, imaging and biopsy.Pharmacologic treatment for breast cancer is selected according to the molecular characteristics of the tumor and the disease stage. Agents used includes,Hormone therapy, HER2-targeted therapy, tyrosine kinase inhibitors, CDK4/6 inhibitors, MTOR inhibitors, PIK3CA inhibitors,Chemotherapy, Immunotherapy.[4] Bilateral breast cancer (BBC) is a rare event accounting in breast malignancies. The risk factors include family history of malignant neoplasms, development of breast cancer at an early age, lobular breast cancer, early stage of development, presence of receptor expression and the type of treatment methods used.[5] A second tumor in the contralateral breast may be either a synchronous or a metachronous lesion. The tumor is defined as a synchronous breast carcinoma (SBC) when contralateral cancer is identified within 6 months after the first breast cancer and as a metachronous breast carcinoma (MBC) if identified after 6 months. The majority of bilateral breast cancers are MBC, while SBC, accounts for 0.2%–2% of bilateral breast cancers.[6]Human epidermal growth factor receptor-2 (HER2/neu, c-erbB2), one of a family of four membrane tyrosine kinases, was found to be amplified in a human breast cancer cell line.(7)HER2 is a membrane tyrosine kinase and oncogene that is overexpressed and gene amplified in about 20% of breast cancers. When activated it provides the cell with potent proliferative and anti-apoptosis signals and it is the major driver of tumor development and progression for this subset of breast cancer. When shown to be overexpressed or amplified by appropriate methods, HER2 is a valuable treatment target. Since that time, HER2 amplification and resultant HER2 protein overexpression have been linked to important tumor cell proliferation and survival pathways; several drugs have been developed to target the pathway and the detection of HER2 has become a routine prognostic and predictive factor in breast cancer.[8]The HER2 pathway is described in terms of, an input layer of membrane receptors and their ligands to trigger the signal coming from outside the cell, a core system processing layer of protein kinases transmitting the signal to the nucleus, and an output layer of transcription factors regulating genes that affect various cellular functions.[9] Transcription factors activated by the pathway regulate many genes involved in cell proliferation, survival, differentiation, angiogenesis, invasion and metastasis.Even estrogen, working via the non-genomic activity of ER outside the nucleus has been shown to activate HER2 signalling.[10] Breast cancers can have up to 25–50 copies of the HER2 gene, and up to 40–100 fold increase in HER2 protein resulting in 2 million receptors expressed at the tumor cell surface.[6]The HER2 expression between normal tissues and tumors helps to define HER2 receptor as an ideal treatment target. Trastuzumab effects are relatively specific for cancer cells overexpressing HER2. [11]Trastuzumab is a monoclonal anti-human epidermal growth factor receptor 2 protein antibody, which is indicated as a first-line treatment for metastatic HER2-overexpressing breast cancer, and as monotherapy in patients who have previously received one or more chemotherapy regimens in the metastatic setting. [12]It works as a mediator of antibody-dependent cellular cytotoxicity, where it binds as an antibody to cells over-expressing HER2, leading to preferential cell death.It binds to the extracellular ligand-binding domain and blocks the cleavage of the extracellular domain of HER-2 to induce its antibody-induced receptor down modulation, subsequently inhibits HER-2-mediated intracellular signaling cascades. Inhibition of MAPK and PI3K/Akt pathways lead to an increase in cell cycle arrest, the suppression of cell growth and proliferation.Trastuzumab also mediates the activation of ADCC by attracting the immune cells, such as natural killer cells, to tumor sites that overexpress HER-2.[13]

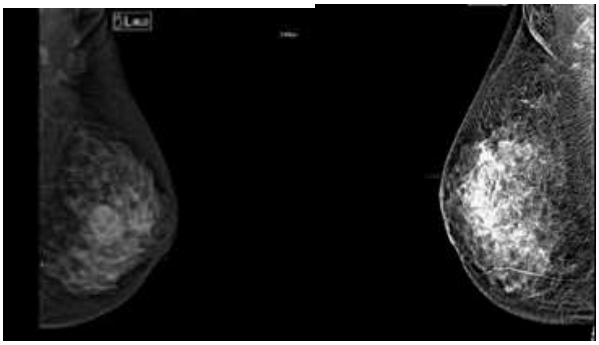
Pertuzumab targets the extracellular dimerization domain (subdomain II) of the protein HER2. It consists of two heavy chains and two lights chains that have 448 and 214 residues respectively. It was first approved by FDA in 2012 for use with docetaxel and another HER2-targeted monoclonal antibody, trastuzumab in the treatment of metastatic HER2-positive breast cancer.It'sused as both a neoadjuvant therapy and an adjuvant therapy in the treatment of HER2-positive breast cancers at high risk of recurrence.[14]Pertuzumab has a relatively long duration of action necessitating dosing every 3 weeks.[15]Here, we report a case of synchronous bilateral breast cancer with different tumor biology right breast HER2 positive and left breast HER2 negative treated with trastuzumab and pertuzumab.

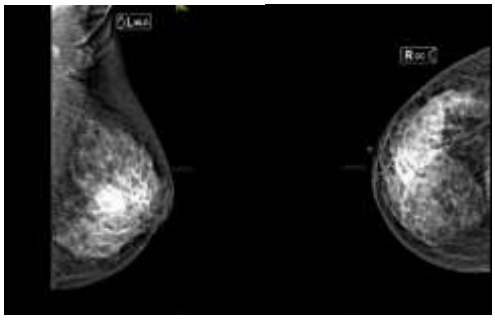
Case Presentation:

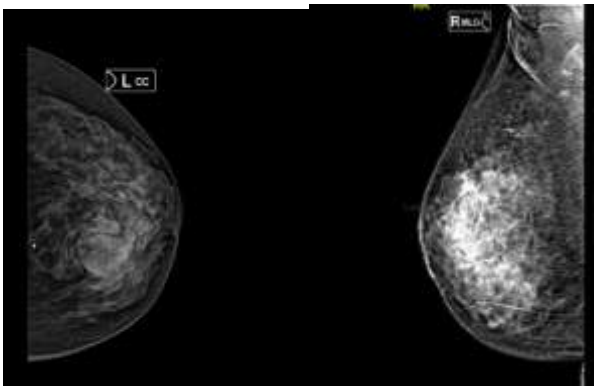
A 51 year old Female patient presented with complaints of lump in the Right Breast since 2 months and on evaluation found to have B/L breast cancer. Patient was tested for BRCA 1, BRCA 2 and TP53 genes, which were negative. Mammography of right breast showed asymmetric density in upper outer quadrant. On HRUS, irregular heterogeneously hypoechoic lesion of 34 x 24 mm with internal vascularity was observed in periareolar region. Few similar morphology lesions seen adjacent to above lesion and in retroareolar region, largest measuring 20 x 8.4 mm were observed [BIRADS –V]. Left breast showed Isodense lesion with calcification in upper inner quadrant. On HRUS, complex solid cystic lesion of 40 x 29 mm was observed. The solid component showed calcification and internal vascularity. The cystic component is predominant and showed mural nodules, largest measuring 10 x 7 mm. Altered echotexture of surrounding parenchyma was observed [BIRADS –IV]. Biopsy showed Invasive carcinoma

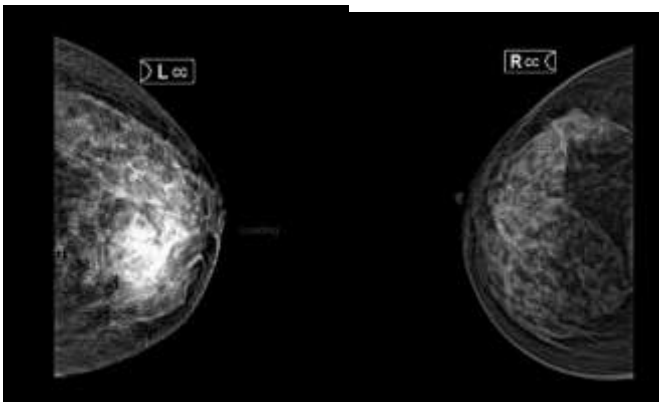
NST, Grade- 2 in both breasts and IHC showed Left Breast-ER-positive (90%), PR-positive (90%), HER 2neu-Negative classified as cT2N0M0, stage I and Right Breast-ER-positive (40%), PR-low positive (10%), HER 2neu-Positive classified as cT2N2M0, stage Ia.PET-CT Metabolically active soft tissue density lesion in right breast upper outer quadrant with adjacent multiple soft tissue densities and cystic component was observed in the left breast.
The patient was administered six cycles of Inj.genexol-PM 260mg Iv, Inj. carboplatin 450mg Iv , Inj. pertuzumab 840mg Iv, Inj. trastuzumab 440mg Iv, Inj. pegasta 6mg-D2 as neoadjuvant chemotherapy.

Post neoadjuvant chemotherapy mammogram showed BIRADS VI residual lesions of both breasts and Right axillary nodes with thickened cortex (SAD 6 mm, residual]. Right modified radical mastectomy, left mastectomy and biopsy was performed. The left breast showed one node which was non-malignant whereas the right breast showed one (out of sixteen lymph nodes) with metastatic tumor deposits. After six months, significant tumor reduction was observed in left breast (ypT1N0 (sn)M0) and complete tumor reduction with residual node was seen in right breast (ypT0N1aM0).As adjuvant therapy, she was administered trastuzumab and pertuzumab as targeted dual-therapy for three cycles, patient did not experience any ADR and had an event freesurvival.



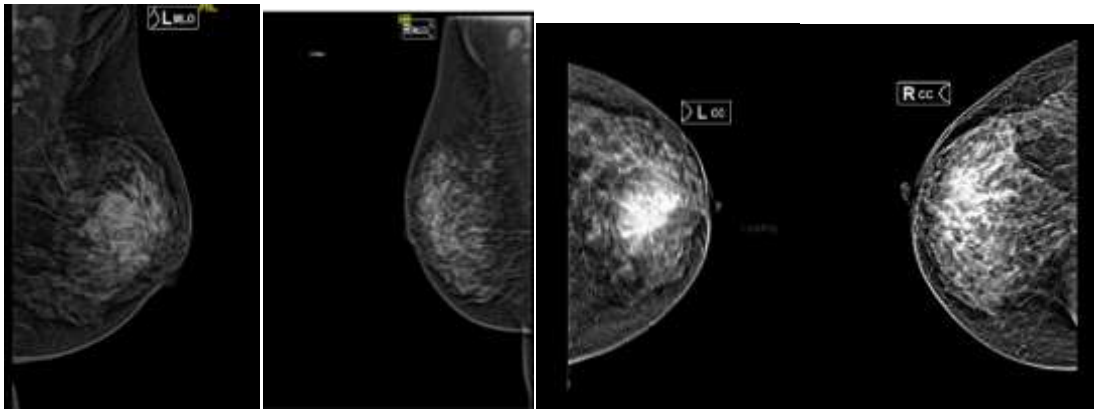


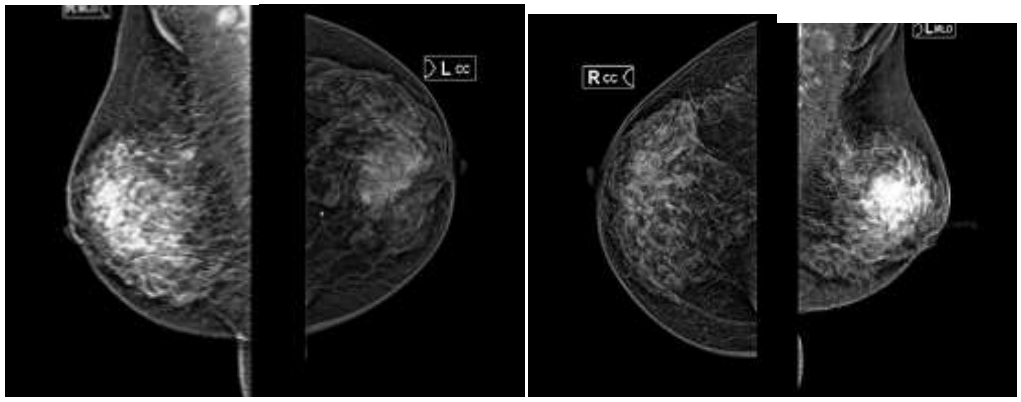




PRE- NACT MAMMOGRAM:

1. Right breast BIRADS -V.
2. Left breast - BIRADS –IV.





POST – NACT MAMMOGRAM:

1. BIRADS 6 residual lesions of both breasts.
2. Right axillary nodes with thickened cortex (SAD 6 mm) - residual.

Discussion:-

Breast cancer is usually associated with local, lymphatic spread and blood–borne spread to lungs, bones and liver. The incidence of synchronous bilateral cancer is of approximately 1 to 2% and that of metachronous cancer is 5 to 6%.[16, 17]Human epidermal growth factor receptor-2 (HER2) is a member of the epidermal growth factor family of tyrosine kinase receptors. This family includes HER1(Erb1), HER3 (Erb3), and HER4 (Erb4) besides HER2[18]. HER receptors are essential for cell proliferation, differentiation, and survival. HER2-amplified breast cancers have unique biological and clinical characteristics such as increased proliferation rates, high histologic and nuclear grade, low ER and PR levels, more aneuploidy, tendency to metastasize to CNS viscera, relative resistance to endocrine

therapy.[19]The patient was administeredTrastuzumab which is a monoclonal antibody. It binds to the extracellular segment of the HER2 receptors. Its mechanism of action is still not fully understood. It seems to have its most significant effects on tumors with increased HER2 homodimers.[20, 21] Although it does not block the auto phosphorylation of HER2, it does inhibit HER2 downstream signallingadditionally, it may disrupt the HER2/Src interaction and enhance antibody-mediated cytotoxicity, induces the immune-mediated response that causes internalization and downregulation of HER2.Fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia are common ADRs of this drug.[22]

Pertuzumab is also a monoclonal antibody. It binds to the extracellular dimerization domain of HER2 and prevents it from binding to itself or other members of the EGFR family. Dosing is in combination with trastuzumab rather than a single agent.[23]Diarrhoea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy are commonly observed ADRs.[24]

Paclitaxel [genexol-PM] is a taxoid chemotherapeutic agent used as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary, and other various cancers including breast and lung cancer. Paclitaxel binds to the β subunit of tubulin. Tubulin is the "building block" of mictotubules, and the binding of paclitaxel locks these building blocks in place. The resulting microtubule/paclitaxel complex does not have the ability to disassemble. Nausea, vomiting, diarrhoea, mouth sores, muscle/joint pain, numbness/tingling/burning of the hands/feet, flushing, dizziness, or drowsiness, temporary hair loss are common ADR's.[25]This adversely affects cell function because the shortening and lengthening of microtubules.Paclitaxel given weekly together with the humanized monoclonal antibody against HER2, trastuzumab, has shown response rates of 50-82% in patients with aggressive HER2-positive tumors.[26]

Carboplatin predominantly acts by attaching alkyl groups to the nucleotides, leading to the formation of monoadducts and DNA fragmenting when repair enzymes attempt to correct the error. 2% of carboplatin's activity comes from DNA cross-linking from a base on one strand to a base on another, preventing DNA strands from separating for synthesis or transcription.[27]Stomach pain, body aches/pain, diarrhea, constipation, weakness, nausea, and vomiting may occur. Nausea and vomiting can be severe in some patients but usually go away within 24 hours of treatment, temporary hair loss are common ADR's.[28]Trastuzumab and carboplatin present high efficacy, safety, and 5-year DFS and OS in HER-2-positive breast cancer patients, and have good recovery effect on inflammation, immune response and oxidative stress.[29]

Pegasta Injection is used to prevent infections after chemotherapy.It is a growth factor that stimulates bone marrow to produce white blood cells. These cells protect the body against infections.The most common side effects of this medicine include e bone pain, joint pain, and headache, nausea, and muscle pain.[30]

After every chemotherapy cycle patient was prescribed Ondansetron (8mg) twice daily for 3 days for nausea/vomiting, pantoprazole (40 mg) once daily for 3 days, loperamide hydrochloride (2 mg) for loose stools, tramadol hydrochloride(37.5mg) and acetaminophen(325mg)for body pains, dicyclomine hydrochloride(20mg) and Paracetamol(500mg) for abdominal pain and multivitamins as supplements.

In this report, the patient was diagnosed with synchronous locally advanced bilateral breast cancers showing different tumor biology, the left breast cancer was hormone receptor (HR)-positive and HER2-negative and the right breast was HR-positive and HER2-positive. The patient had grade 2 tumor in both breasts, and increased nodal metastases was observed in HER2 positive right breast hence, trastuzumab and pertuzumab were administered as dual therapy for NAC and it showed complete tumor reduction with residual nodes in right breast, whereas the left breast showed partial response post- surgery. Neoadjuvant combination of trastuzumab and chemotherapy resulted in partial response inHER2 positive right breast.

References:-

1. **Chen**, Y., Thompson, W., Semenciw, R. & Mao, Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol. Biomarkers Prev. 8, 855–861 (1999).
2. **Hartman**, M. et al. Incidence and prognosis of synchronous and metachronous bilateral breast cancer. J. Clin. Oncol. 25, 4210–4216 (2007).
3. https://www.who.int/news-room/fact-sheets/detail/breast-cancer

4. https://emedicine.medscape.com/article/1947145
5. **Carmichael** AR, Bendall S. The long–term outcome of synchronous bilateral breast cancer is worse than metachronous or unilateral tumours. Eur J Surg Oncology. 2002.
6. https://www.liebertpub.com
7. King CR, Kraus MH, Aaronson SA. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science. 1985 Sep 6;229(4717):974–976
8. HER 2: Biology, Detection, and Clinical Implication Carolina Gutierrez, M.D. and Rachel Schiff, Ph.D
9. Citri A, Yarden Y. EGF-ERBB signalling: towards the systems level. Nat Rev Mol Cell Biol. 2006 Jul;7(7):505–516
10. Shou J, Massarweh S, Osborne CK, et al. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. J Natl Cancer Inst. 2004.
11. . Kallioniemi OP, Kallioniemi A, Kurisu W, et al. ERBB2 amplification in breast cancer analyzed by fluorescence in situ hybridization. Proc Natl AcadSci U S A. 1992 Jun.
12. FDA Approved Drug Products: Herceptin (trastuzumab) for intravenous injection.
13. Albanell J, Codony J, Rovira A, Mellado B, Gascon P: Mechanism of action of anti-HER2 monoclonal antibodies: scientific update on trastuzumab and 2C4.
14. FDA Approved Drug Products: Perjeta (pertuzumab) for intravenous injection.
15. Health Canada Product Monograph: Perjeta (pertuzumab) for intravenous injection.
16. Vuoto, H. D. et al. Bilateral breast carcinoma: clinical characteristics and its impact on survival. Breast J. 16, 625–632 (2010).
17. Sakai, T. et al. National trends of synchronous bilateral breast cancer incidence in the United States. Breast Cancer Res. Treat. 178, 161–167 (2019).
18. www.ncbi.nlm.nih.gov/books/NBK537134
19. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. Nida Iqbal and Naveed IqbalPublished 2014 Sep 7 PMCID: PMC4170925 PMID: 25276427
20. Vu T, Claret FX. Trastuzumab: updated mechanisms of action and resistance in breast cancer. Front Oncol. 2012.
21. Targeted therapy in HER2-positive
    Breast cancer. Shu Guang li and li li
    2013 Jul; 1(4): 499–505. Published
    2013 Apr 18 doi 10.3892/br.2013.95
    PMCID: PMC3917005.
22. https://www.herceptin.com/hcp/metastatic-breast-cancer/side-effects
23. https://go.drugbank.com/drugs/DB06366
24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4093365
25. https://www.webmd.com/drugs/2/drug-3477/paclitaxel.
26. https://pubmed.ncbi.nlm.nih.gov/12505596
27. https://go.drugbank.com/drugs/DB00958
28. https://www.webmd.com/drugs/2/drug-4551/carboplatin
29. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7039112
30. https://www.1mg.com/drugs/pegasta-injection-118588.