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Trastuzumab Induced Cardiotoxicity - A Case Series

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ABSTRACT

Trastuzumab has become the treatment of choice for HER-2+ metastatic breast cancer with increased progression free survival and overall survival compared to conventional chemotherapy treatment. Unfortunately, cardio toxicity was reported from western countries following Trastuzumab and Pertuzumab therapy. We describe 4 case studies where patients developed cardiotoxicity following treatment with Trastuzumab and its management. Additive effect of pertuzumab on cardiac dysfunction was observed especially in patients with prior long-term trastuzumab treatments. Pertuzumab when co-administered with trastuzumab worsen the scenario by causing a progressive decline in LV ejection fraction within a shorter follow-up timeline. In all four cases there were significant reduction in Left ventricular ejection fractions and it was reversed when Lapatinib was substituted for trastuzumab and with additional medications betablocker and Ivabradine. Evaluation of risk factors for cardiac toxicity before initiation and periodic monitoring of cardiac functions need to be conducted especially left ventricular ejection fraction as early withdrawal of trastuzumab and appropriate remedial measures could reverse the cardiac toxicity in Indian population as well.

INTRODUCTION

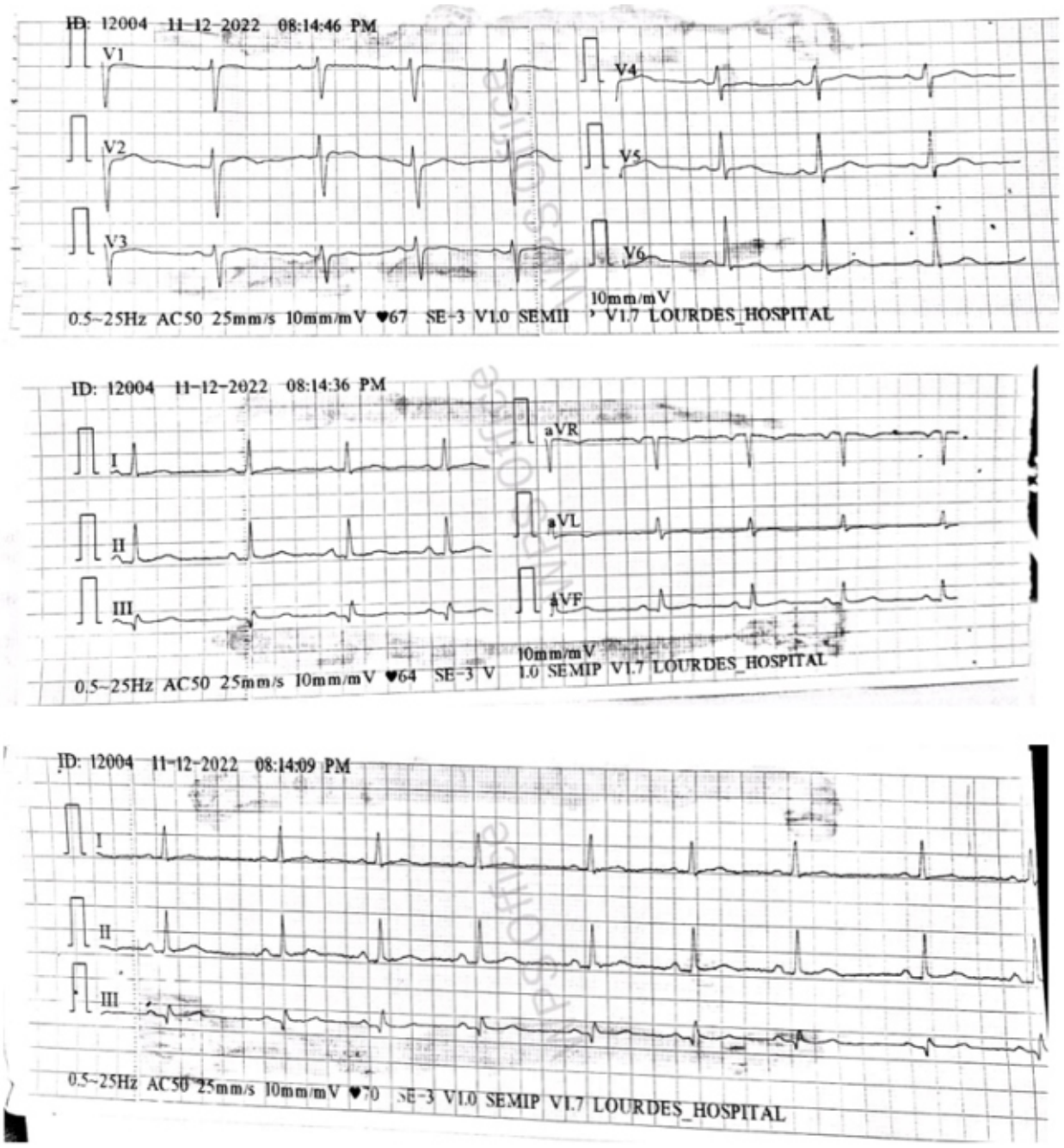
The recombinant humanized IgG1 monoclonal antibody is beneficial for patients with over expression or amplification of HER-2 oncogene. Trastuzumab is the standard treatment of choice for HER-2+ metastatic breast cancer and also for adjuvant management of localized HER-2+ breast cancer. Trastuzumab in combination with standard chemotherapy showed much improvement in disease-free survival rate in these patients.[1]. Likely, the survival rate was significantly prolonged with the use of another anti-HER2 drug called Pertuzumab.[2]

Unfortunately, cardiotoxicity is frequently reported in approximately 10% of the patients, with a higher incidence when both of these antibodies are used concurrently. [3] Manifestations include left ventricular dysfunction, arrhythmias, Cardiacfailure, cardiomyopathy and diastolic dysfunction. However, most of these toxicities especially those from trastuzumab is reversible and not dose dependant. Risk factors include elderly, those with comorbidities like diabetes mellitus, hypertension, decreased glomerular filtration rate and history of heart disease.[4]Here,we describe 4 case studies where patients developed cardiotoxicity following treatment with Trastuzumab and its management.

CASE 1

A 73-year old woman with multiple comorbidities was diagnosed with follicular lymphoma grade 3,stage 4.She was treated with 6 cycles of chemotherapy- Rituximab and Bendamustine. she noticed a swelling over the right breast after 6 cycles of chemotherapy. Ultrasonography showed irregular hypoechoic hard solid lesion on right breast ACR-BIRADS-category 4C. Right Modified Radical Mastectomy was done and histopathology result showed Grade 2,right breast residual invasive carcinoma of no special type(ductal, not otherwise specified). Biopsy showed the tumour to be Estrogen receptor positive, progesterone receptor negative and HER 2 positive

She was treated with trastuzumab, letrozole and other supportive care drugs. A screening echocardiogram conducted during the same month showed left bundle branch block, however had a preserved LV ejection fraction of 54%.Immediately following the 6th cycle of chemotherapy with trastuzumab



infusion, she developed breathing difficulty on exertion for which she was admitted in the cardiac care unit. On clinical examination, she was afebrile with a blood pressure of 140/90mmHg and a heart rate of 120 b.p.m. ECG showed ST-T changes (Figure 1) and cardiac biomarkers remained negative [HS troponin I-6.9ng/L]. Echocardiogram demonstrated that the patient had severe LV Systolic dysfunction with an ejection fraction of 15%,LV dp/dt - 478 mmHg/sec along with basal inferior wall contracting and all other segments severely hypokinetic. Also diagnosed with Aortic Valve Sclerosis and Grade 1 Diastolic dysfunction.

Patient was managed with standard cardiac medications including antiplatelets, statin, betablocker, digoxin, diuretics and ivabradine. As cardiotoxicity was suspected to be chemotherapy with trastuzumab, It was discontinued as suggested by the cardiologist. She was started on Lapatinib for ongoing management of malignancy. A repeat echocardiography 6 months post-admission demonstrated slight improvement in left ventricular ejection fraction to 25%[>10% improvement from the previous report].

CASE-2

This is a case of progressive decrease in LV ejection fraction in a 50-year old female with HER-2 positive (score 3+),ER and PR positive (Allred scoring)invasive carcinoma breast with multiple metastasis following chemotherapy with Trastuzumab. On physical examination she had enlarged multiple nodes in right cervical region, enlarged right axillary lymph nodes, nipple retraction and cervical lymphadenopathy. Mammogram showed irregular opacity of the right breast. USG guided FNAC from lesion in the right breast confirmed the tumour to be invasive carcinoma. Biopsy taken from upper deep cervical lymph node

confirmed metastatic carcinoma. PET-CT reports were conclusive of multiple metastasis.

Her initial treatment included Modified Radical Mastectomy followed by chemotherapy with Cyclophosphamide and Doxorubicin for first3 cycles then Doxorubicin was replaced with docetaxel and continued till 6th course cycle. From seventh cycle till 24th cycle only Trastuzumab was given. Pertuzumab and docetaxel were added to the regimen from 25th cycle onwards. After 27thcycle patient started to develop complaints of chest discomfort and underwent an ECHO and Doppler test. She was conscious, oriented with a heart rate of 96 b.p.m and blood pressure of 110/80mmHg.The reports showed adequate LV systolic function: 55%,No RWMA and Grade 1 diastolic dysfunction and was recommended to repeat ECHO after 2 months. Follow-up echocardiography after 2 months revealed a progressive decline of LV ejection fraction to 45%. ECHO and Doppler reported hyperkinesia of apical IVS ,apical anterior wall and apex and mild LV systolic dysfunction .Patient was admitted in the cardiac care unit for Coronary Artery Angiography in view of echo showing mild LV systolic dysfunction. In view of cardiac toxicity, chemotherapy with trastuzumab and pertuzumab were discontinued and lapatinib, capecitabine and letrozole were prescribed. She was prescribed with Ivabradine and betablocker for medical management of associated complaints.

CASE -3

A 51-year old female patient presented with complaints of swelling right breast for 4 months duration. She was diagnosed with infiltrating ductal carcinoma and underwent Right Modified Radical Mastectomy. Her initial treatment involved 6 courses of chemotherapy with Docetaxel, Epirubicin and Cyclophosphamide followed by radiation treatment. Later on, 11 cycles of targeted therapy with Trastuzumab were initiated.

During this period, she had complaints of frequent episodes of breathlessness and was referred for cardiology consultation. The patient was conscious, oriented, afebrile with a blood pressure of 130/80 mmHg and pulse rate of 80 b.p.m. The echocardiography reports showed moderate LV systolic dysfunction with a reduced ejection fraction of 38%, and global hypokinesia of LV. She was managed with digoxin, betablocker, diuretics and bronchodilator.

Cardiologist suggested to stop trastuzumab therapy. Soon after, she was started on alternative anti-HER2 therapy with lapatinib. Repeat ECHO and Doppler studies after 4 months revealed significant improvement in LV ejection fraction to 62% so a complete resolution of cardiomyopathy was evident from this follow-up report.

CASE-4

This is the case of a 45-year old female patient diagnosed with HER 2+ve carcinoma right breast. Modified radical mastectomy was done and the histopathology report was suggestive of invasive carcinoma with a tumour size of 2.1x1. 5x2cm.Initially she was started with trastuzumab based regimen.

Baseline Echocardiography taken prior to this therapy showed a preserved cardiac function with normal LV systolic function (LVEF-60%) and no RWMA. Following the 7th cycle of chemotherapy with trastuzumab, a repeat echo and Doppler test was conducted. The results shown severe LV systolic dysfunction with an ejection fraction of 20%,global LV hypokinesia and Grade 1 diastolic dysfunction. Oncologist discontinued chemotherapy with trastuzumab in the view of severe cardiac dysfunction.

Later on, she was started with Tab. tamoxifen along with radiation therapy. Fortunately, five months later her LV ejection fraction was found to be significantly improved to 50% i.e 30% increase upon discontinuation of the drug. This case is also an example of complete reversal of cardio toxicity induced by trastuzumab.

DISCUSSION

Monoclonal antibodies are one of the most effective therapeutic options for cancer patients[5];especially beneficial for patients with overexpression or amplification of HER 2 oncogene.[1]However these pose a high risk of cardiac toxicities often manifested as hypertension, QT interval prolongation, left ventricular dysfunction, observed both during and after therapy.[5]Trastuzumab disrupts HER signalling by inducing phosphorylation of HER1 and HER2 at 845 and 1248 sites, respectively, and activates autophagy-inhibitory Erk/mTOR/Ulk 1 signalling cascade, thereby compromising cardiomyocyte's ability to recycle toxic cellular substrates causing cardiotoxicity [6] With the use of strategies like cardiovascular screening and traditional biomarker detection routinely while on these therapies would improve the safety and efficacy of cancer chemotherapy. Comparison of clinical features of study subjects are given in table No:1

Significant cardiac events observed while on trastuzumab was symptomatic or asymptomatic decline in left ventricular ejection fraction; however these events could be reversed and managed to a certain extend.[7] Older age is a risk factor for trastuzumab induced cardiotoxicity considering the fact that these population tend to have higher cardiovascular disease and other comorbidities in general.[8] Likewise, in the first case study, the elderly patient with multiple comorbidities developed a drastic decline in LV ejection fraction to 15% after completion of 6 cycles of therapy. Baseline LVEF prior to the start of chemotherapy showed a preserved LV Systolic function with an ejection fraction of 54%. Cessation of the regimen improved LVEF to 25% i.e>10% from the previous report; clearly depicting that trastuzumab had hastened the worsening of LV systolic function.

Additive effect of pertuzumab on cardiac dysfunction was observed especially in patients with prior long-term trastuzumab treatments.[3] Moreover, multiple monoclonal antibodies when used concurrently developed cardiotoxicity as evident in the second case study. Here, pertuzumab when co-administered along with trastuzumab worsened the scenario by causing a progressive decline in LV ejection fraction within a shorter follow-up timeline.i.e from ejection fraction of 55% to 45%(>10% reduction).

Cardiotoxicity with trastuzumab is mostly reversible and is therefore categorized as causing type II chemotherapy related cardiac dysfunction.[8] Likewise Case study 3 and 4 depicts complete reversal of LV systolic function after discontinuing the intolerant drug. (In 3rd case-LV ejection fraction from 38% to 62% within a time span of 4 months and in the 4th case-LV ejection fraction from 20% to 50% within a time period of 5 months)

CONCLUSION

Based on the above case studies, before starting chemotherapy Trastuzumab, risk factors for cardiac toxicity must be taken into consideration and treatment with alternative or less cardiotoxic drug must be initiated. In addition, routine follow-up

Table 1 : Clinical characteristics of study subjects

Clinical features	Patient 1	Patient 2	Patient 3	Patient 4
Age in years	73	50	51	45
Gender	Female	Female	Female	Female
Presenting symptoms				
breathing difficulty on exertion	+		+	
chest discomfort		+		
Blood pressure **mmHg**	**140/90**	**110/80**	130/80	
Heart rate **b.p.m**	**120**	96	80	
ECG	**ST-T changes**			
Echocardiogram				
LVEF baseline	**54%.**	**55%**		60%
LVEF during treatment	**15%**	**45%**	38%	20%
LVEF after stopping Trastuzumab	**25%**	NA	62%	50%
Trastuzumab was changed to lapatinib	+	+	+	
Medications used to improve LVEF				
Betablocker	+	+	+	+
Ivabradine	+	+	–	-

examinations must be carried out in those with longer-duration of treatment plan to monitor for the development of cardiotoxicity during and after anticancer treatment. Early diagnosis can facilitate immediate withdrawal or discontinuation of the drug thereby reversing the associated toxic effects with the help of standard cardiac medications.

REFERENCE

1. Boekhout AH, Beijnen JH, Schellens JH. Trastuzumab. The oncologist. 2011 Jun;16(6):800-10.
2. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, Ciruelos E, Schneeweiss A, Loi S, Monturus E, Clark E. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. The Lancet Oncology. 2020 Apr 1;21(4):519-30.
3. Ito M, Horimoto Y, Sasaki R, Miyazaki S, Orihata G, Saito M. Cardiotoxicity after Additional Administration of Pertuzumab following Long-Term Trastuzumab: Report of 2 Cases. Case Reports in Oncology. 2021;14(1):62-6.
4. Cardiotoxicity: An Unexpected Consequence of HER2-Targeted Therapies - American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2016/06/06/09/32/cardiotoxicity (assessed July 15 2023)
5. Brown LJ, Meredith T, Yu J, Patel A, Neal B, Arnott C, Lim E. Heart Failure Therapies for the Prevention of HER2-Monoclonal Antibody-Mediated Cardiotoxicity: A Systematic Review and Meta-Analysis of Randomized Trials. Cancers. 2021 Nov 3;13(21):5527.
6. Mohan, N, Shen, Y, Endo, Yet al. Trastuzumab, but not pertuzumab. dysregulates HER2 signaling to mediate inhibition of autophagy and increase in reactive oxygen species production in human cardiomyocytes. *Mol Cancer Ther*2016; 15: 32131
7. Kumar M, Thangavel C, Becker RC, Sadayappan S. Monoclonal antibody-based immunotherapy and its role in the development of cardiac toxicity. Cancers. 2021 Jan;13(1):86.

8. Onitilo AA, Engel JM, Stankowski RV. Cardiovascular toxicity associated with adjuvant trastuzumab therapy: prevalence, patient characteristics, and risk factors. Therapeutic advances in drug safety. 2014 Aug;5(4):154-66.

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