International Journal Dental and Medical Sciences Research
Volume 5, Issue 1, Jan-Feb 2023 pp 314-317 www.ijdmsrjournal.com ISSN: 2582-6018

Analysis on the effectiveness of dual blockade of her 2 receptor using Pembrolizumab and Trastuzumab in Metastatic Breast Cancer in Indian scenario - A case report and review of literature

Dr Anmol Mahani

Submitted: 17-01-2023 Accepted: 31-01-2023

I. INTRODUCTION

Breast cancer constitutes one the most common malignancies in the country which affects a person not only physically but also psychologically. Management of Breast cancer is a multimodality approach which includes surgery, chemotherapy, radiotherapy, hormonal therapy etc. A very important factor known as Human epidermal growth factor receptor type 2 (HER2) has been studied in great details in various literatures. The development of monoclonal antibodies against HER2 has revolutionized the treatment of HER2-positive breast cancer which initially was considered a poor prognostic factor. The humanized monoclonal antibody, trastuzumab, was the first in its class to be widely studied and brought into practice. It was initially studied in the metastatic setting and then in the treatment of early-stage disease, and had played a pivotal part in either scenario. HER2 is unique to other members of the HER family as it can constitutively dimerize without ligand binding. It forms homodimers and heterodimers with other epidermal growth factor receptor (EGFR) proteins leading to downstream activation of multiple pathways, The HER2-HER3 heterodimers likely promotes the strongest signal transduction, particularly via the PI3K/AKT/mTOR pathway.2 HER2 is over expressed in 15 to 20% of all invasive breast cancers. The addition of pertuzumab further improved upon results achieved with trastuzumab and chemotherapy, specifically extending overall survival in patients with metastatic disease, lessening the risk of recurrence when used in the adjuvant setting, and improving pathologic complete response rate when utilized in the neoadjuvant setting.

Evolution of Trastuzumab

Trastuzumab was the first recombinant humanized monoclonal antibody that dramatically changed the treatment of HER2-positive breast cancer worldwide. Initially, Her 2 neu positivity was associated with poor prognosis due to chances of early metastases, decreased disease-free survival (DFS), and decreased overall survival (OS). Trastuzumab was first approved by the US Food and Drug Association (FDA) in 1998 to treat patients with metastatic breast cancer whose tumors over express the HER2 protein and who have received at least one chemotherapy regimen for metastatic disease. According to a landmark trial conducted by Slamon et al, the benefit of adding trastuzumab to chemotherapy (anthracycline and Cyclophosphamide or Paclitaxel) in the first-line metastatic setting was seen. The addition of trastuzumab to chemotherapy improved the median time to progression to 7.4 months compared to 4.6 months in the chemotherapy alone group ($p<0.001$).

With such miraculous effect, the trastuzumab had its disadvantages as well. The most concerning of which is cardio toxicity. According to the literature, New York Heart Association (NYHA) class III or IV heart failure occurred in up to 27% of patients treated with anthracycline, Cyclophosphamide, and trastuzumab. Therefore, assessment of left ventricular ejection fraction (LVEF) is recommended every 3 monthly while using Trastuzumab.

Role of Pertuzumab

Pertuzumab is a HER2-targeted monoclonal antibody that belongs to the class of HER dimerization inhibitors. It binds to a different domain of HER2 than trastuzumab resulting in prevention of HER2/HER3 heterodimerization and homodimerization. The landmark trial also known as The Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) studied 808 breast cancer patients and demonstrated the added benefit of pertuzumab to trastuzumab and Docetaxel in the first-line metastatic setting. The studied showed that the median overall survival increased from 40.8 months with Docetaxel and trastuzumab alone to 56.5 months with pertuzumab added to Docetaxel and trastuzumab.. Remarkably, at 8-years of long-term follow-up, 37% of patients with

International Journal Dental and Medical Sciences Research
Volume 5, Issue 1, Jan-Feb 2023 pp 314-317 www.ijdmsrjournal.com ISSN: 2582-6018

metastatic disease treated with the combination were still alive This regimen was established as the standard of care for first-line treatment of HER2-positive metastatic breast cancer.

The advantage of Pertuzumab is that unlike trastuzumab, the incidence of cardio toxicity is not increased. The other adverse effect of concern is Diarrhea as was demonstrated in the CLEOPATRA trial also. The incidence of all grade diarrhea was 68% in patients treated in the pertuzumab arm versus 49% in the placebo arm.

Clinical History

The patient is a 39 years old female presented with complaints of lump in her right breast for 3 months. The female had no history of any significant malignancy in the family in first degree or second degree relatives, she is a mother of 2 beautiful daughters, youngest one being 6 years of age, with adequate duration of breast feeding and no history of alcohol consumption.

After a complete history and physical examination of the patient, radiological and Histopathological assessment was done. The patient was diagnosed to a be clinically T2N1M0 staged, infiltrating ductal breast cancer with Immunohistochemistry report depicting ER positive, PR positive and Her 2 neu 3 positive and proliferative index of 70 percent . The patient underwent Right Modified Radical Mastectomy with level I – III axillary lymph node dissection, and was staged pathologically T2N1M0. The patient received four cycles of anthracycline based chemotherapy (Adriyamycin in the dose of 60 mg/m2 on day one and Inj Cyclophosphamide 600mg/m2 on day 1 every 3 weekly) followed by four cycles of taxane (Inj Paclitaxel in the dose of 175 mg/m2 every 3 weekly). The patient received adjuvant radiotherapy with 17 cycles of maintenance Inj Trastuzumab (in the dose of 8 mg/kg loading dose followed by 6 mg/kg maintenance dose every 3 weekly). Following the primary treatment, the patient was on follow up along with hormonal therapy of Tamoxifen in the dose of 20 mg once daily

After 2 years of regular follow up, the patient presented with complaints of shortness of breath.

PET CT Scan was done which showed FDG avid deposits in almost entire lung pleura largest measuring 5.2 x 2.6 x 4.3 cm (SUV max 11.28). |Fat stranding and ulceration in right chest wall was seen with significant uptake. Multiple mediastinal lymph nodes likely to be metastatic was also seen.

The case was discussed in the multi department tumor board and patient was planned for Trastuzumab (8 mg/kg loading dose followed by 6 mg/kg maintenance dose) , Pertuzumab (in the dose of 840 mg) and Docetaxel (in the dose of 75 mg/m2) based chemotherapy.

The patient received 7 cycles of the same

Response assessment after 7 cycles of targeted therapy was done with PET CT Scan which has shown complete resolution of all the previous metabolically active lesions.

II. DISCUSSION

Breast cancer constitutes one the most common malignancies in the country which affects a person not only physically but also psychologically. Management of Breast cancer is a multimodality approach which includes surgery, chemotherapy, radiotherapy, hormonal therapy etc. A very important factor known as Human epidermal growth factor receptor type 2 (HER2) has been studied in great details in various literatures. The HER family plays an important role in cell survival and

Proliferation. Over expression of HER2 is associated with poor Prognosis. The humanized monoclonal antibody, trastuzumab, was the first in its class to be widely studied and brought into practice. It was initially studied in the metastatic setting and then in the treatment of early-stage disease, and had played a pivotal part in either scenario. Both pertuzumab and trastuzumab are humanized monoclonal antibodies targeting HER2 and have proven to offer survival benefit for women with HER2-positive breast cancer. Several mechanisms have been proposed to explain the synergism of pertuzumab and trastuzumab in treating HER2- positive breast cancer. The addition of pertuzumab further improved upon results achieved with trastuzumab and chemotherapy, specifically extending overall survival in patients with metastatic disease, lessening the risk of recurrence when used in the adjuvant setting, and improving pathologic complete response rate when utilized in the neoadjuvant setting. Pertuzumab binds HER2 in domain II, a different domain than trastuzumab, and preferentially blocks the heterodimerization of HER2 with EGFR, HER3, and HER4, and the downstream signaling pathways activated by HER2 heterodimers, which activates several intracellular signaling cascades, including cell proliferation and survival.

Therefore, the combination of the two antibodies could Synergistically enhance the blocking effect of the downstream signaling, resulting in greater antitumor activity. The

International Journal Dental and Medical Sciences Research
Volume 5, Issue 1, Jan-Feb 2023 pp 314-317 www.ijdmsrjournal.com ISSN: 2582-6018

combination of pertuzumab with trastuzumab and chemotherapy has been approved both by FDA and the European Medicines Agency in the metastatic, neoadjuvant, and adjuvant settings. According to various literature, Progression free survival (PFS) has been widely used as a primary endpoint. According to CLEOPATRA trial, Progression free survival (PFS) was significantly improved with pertuzumab plus trastuzumab plus Docetaxel, which was first approved in June 2012 by the FDA for the first-line treatment of HER2-positive metastatic breast cancer. After one additional year of follow-up, the Overall survival (OS) analysis also demonstrated statistically significant and clinically meaningful survival benefit with this combination compared with trastuzumab plus Docetaxel, which was maintained after a median follow-up of more than 8 years. In PHEREXA study, it did not show consistency between Progression free survival and Overall survival in advanced breast cancer. It was found that adding pertuzumab to trastuzumab and capecitabine modestly increased PFS, but there was no statistical significance. Although the median OS was increased by using two anti-HER2 regimens, the statistical significance of OS could not be claimed. Combining trastuzumab and pertuzumab in neoadjuvant therapy in the NeoSphere trial resulted in a pCR rate of 45.8% and was significantly superior to neoadjuvant chemotherapy plus trastuzumab alone. However, a 5-year. survival analysis of this trial did not show any significant differences between the two groups (HR = 0.69; 95% CI: 0.34–1.40). Two further neoadjuvant treatment trials reported that the pCR rate in patients treated with dual blockade was approximately twice as high as that in patients with trastuzumab single-agent therapy. A meta-analysis by Chen et al. confirmed that trastuzumab plus pertuzumab significantly improved the pCR compared to trastuzumab in neoadjuvant settings (OR = 1.33; 95% CI:1.08–1.63; p = 0.006). Although dual anti-HER2 therapies were associated with an efficacy benefit in HER2-positive breast cancer, they could increase the risk of cardiac toxicity in previous trials. The FDA recommendations for pertuzumab and trastuzumab limit their use to patients whose LVEF prior to treatment is below 50% or 55%. Other adverse effect of Pertuzumab is diarrhea.

Therefore it has been approved by various literatures that a dual blockade with pertuzumab and trastuzumab holds a very strong position in the treatment line of metastatic breast cancer.

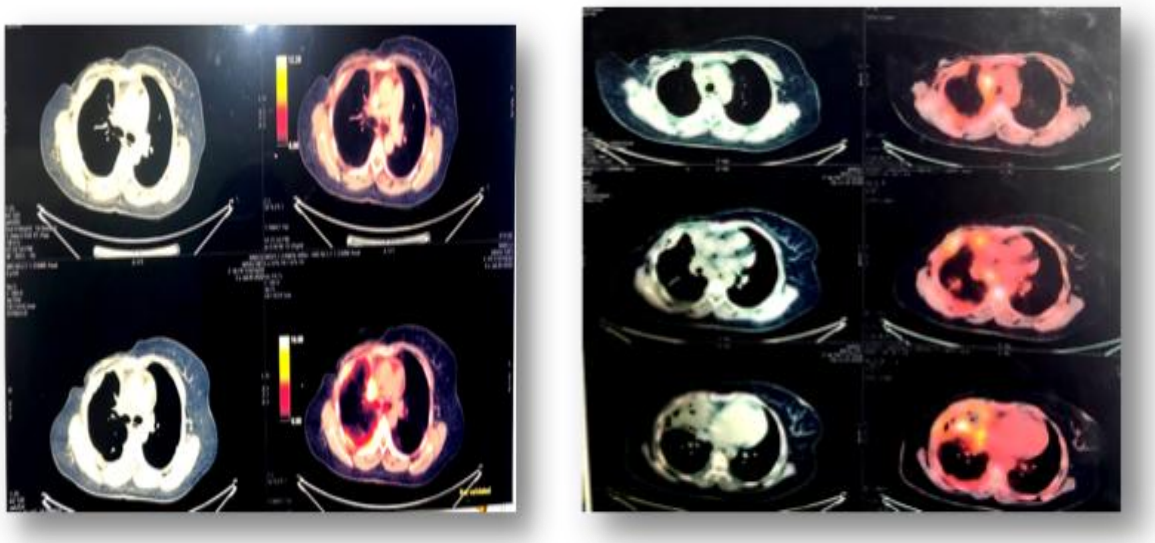

Figure 1a and b showing PET CT scan depicting FDG avid deposits in almost entire lung pleura, largest measuring 5.2 x 2.6 x 4.3 cm (SUV max 11.28). |Fat stranding and ulceration in right chest wall is shown is figure 1b with significant uptake. Multiple FDG avid mediastinal lymph nodes likely to be metastatic

International Journal Dental and Medical Sciences Research
Volume 5, Issue 1, Jan-Feb 2023 pp 314-317 www.ijdmsrjournal.com ISSN: 2582-6018

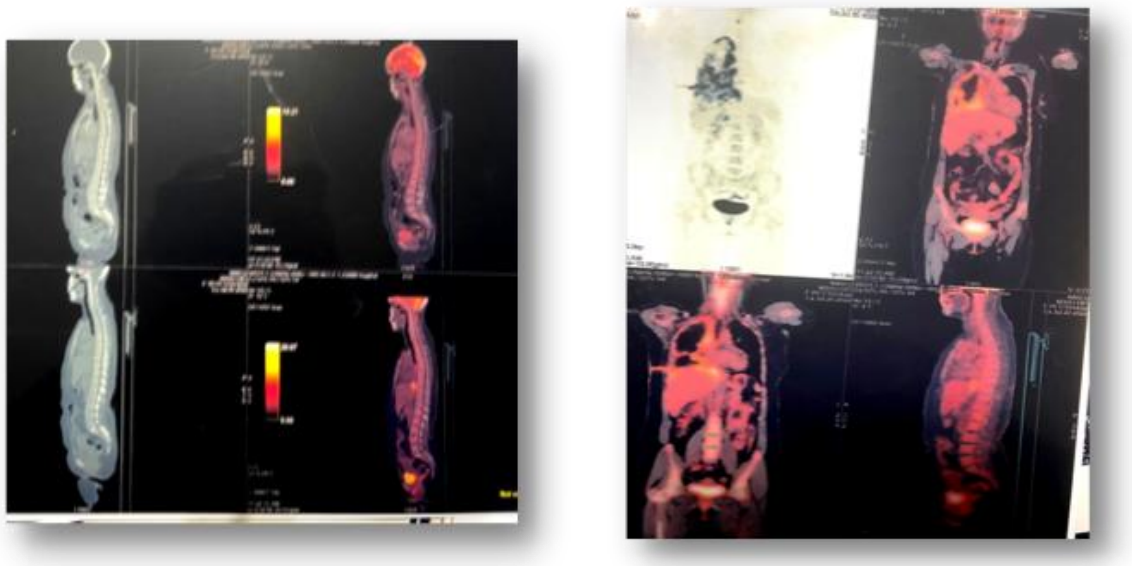

Figure 2a and b showing PET CT Scan image after 7cycles of dual blockage chemotherapy with Trastuzumab and Pembrolizumab, showing complete resolution of previous metabolically active lesions