A 24-month Retrospective Analysis of Cardiotoxicity of the HER2 - Targeted Therapies; Trastuzumab, Pertuzumab & ado-Trastuzumab emtansine in Metastatic Breast Cancer

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Introduction

- The human epidermal growth factor receptor - (HER2-) targeted agents trastuzumab, pertuzumab, and ado-trastuzumab emtansine (TDM-1) have revolutionised breast cancer treatment. HER2 overexpression is linked to an aggressive form of breast cancer that is associated with a decreased time to recurrence and survival.
- HER2 targeted agents are associated with cardiotoxicity. The exact mechanism behind trastuzumab-induced cardiotoxicity (TIC) has not been fully elucidated, it is believed however, that the most plausible hypothesis to date involves the neuregulin (NRG) - ERBB axis (see fig.1).

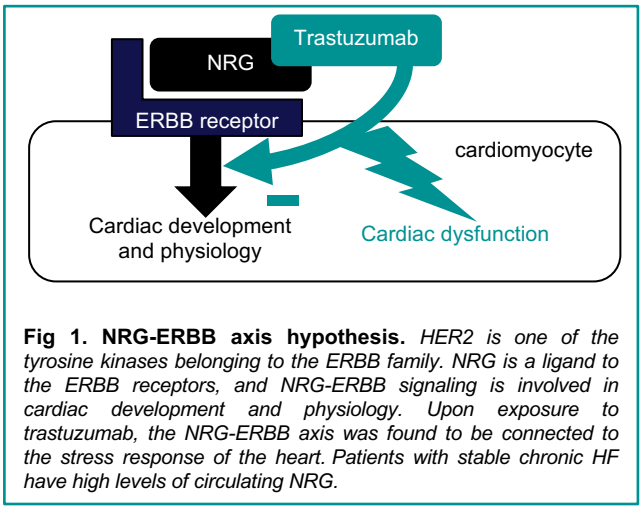

Fig 1. NRG-ERBB axis hypothesis. *HER2 is one of the tyrosine kinases belonging to the ERBB family. NRG is a ligand to the ERBB receptors, and NRG-ERBB signaling is involved in cardiac development and physiology. Upon exposure to trastuzumab, the NRG-ERBB axis was found to be connected to the stress response of the heart. Patients with stable chronic HF have high levels of circulating NRG.*

- Trastuzumab appears to cause myocardial dysfunction (not damage), has a high likelihood of reversibility, is not dose dependent, and carries a low likelihood of late sequential stress-related cardiac dysfunction. In addition, rechallenge can be possible depending on the clinical scenario.
- The greatest risk of TIC is in patients receiving concurrent anthracycline. Other risk factors for TIC include older age, diabetes mellitus, decreased glomerular filtration rate, hypertension, and history of heart disease. Studies have suggested that impaired left ventricular (LV) dysfunction and low baseline LV ejection fraction (LVEF) are also risk factors for cardiotoxicity.

Aims and Objectives

- To compare the cardiotoxicity profiles of HER2-Targeted therapies (trastuzumab, pertuzumab, alone or in combination, and TDM-1) in clinical practice within the Metastatic Breast Cancer (mBC) setting at Leaders in Oncology Care (Harley Street & the Wellington Hospital), London.
- Establish the correlation with risk factors for TIC in these patient subgroups.
- To determine appropriateness of cardio-toxicity assessment whilst on HER-2 therapy for cardiac risk factors.
- To generate a best practice consensus recommendation document for a systematic cardiac evaluation and clinical management of patients on targeted therapies for HER-2 positive breast cancer at LOC.

Method

- This retrospective analysis was conducted in 119 patients with HER-2 positive metastatic breast cancer, who received either trastuzumab (alone or in combination with pertuzumab) or TDM1 over a 2 year period.
- Data collected evaluated full medical history including prior exposure to anthracyclines, left mediastinal radiotherapy and ER and PR receptor status. Cardiotoxic occurrences including hypertension, pericarditis, and thrombosis. LVEF pre- and post treatment were also recorded. Cardiotoxicity was measured as a LVEF of 50% or a drop of ≥ 10%.
- Other data on file includes age and body mass index (BMI).
- Data was extracted from MOSAIQ® electronic records.

Results (see fig 2 – 4.)

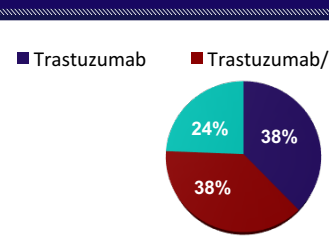

Fig 2. Patient distribution by treatment n=119

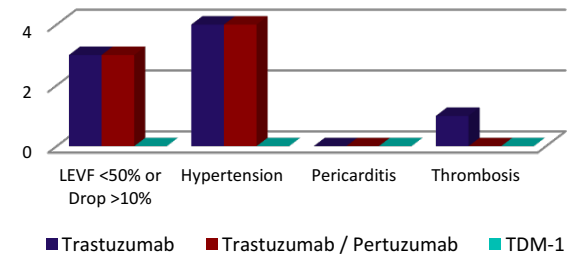

Fig 3. Cardiotoxicity / cardiotoxic occurrences per treatment group

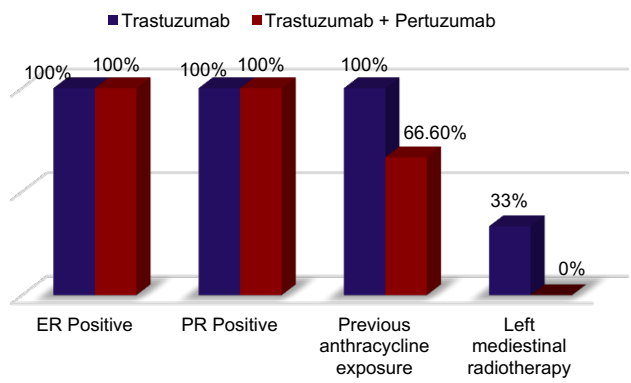

Fig 4. Correlation between past medical history / risk factors and cardiotoxicity in the TIC subgroups

Discussion & Conclusions

- No cardiotoxicity was recorded in the TDM-1 subgroup (29 patients) over a 2 year period regardless of age, BMI, previous exposure to anthracyclines or radiotherapy. Current practice in our centres is to measure LEVF every 3 months as per licensed recommendations of the UK Kadcyla® summary of product characteristics (SmPC).
- In the trastuzumab +/- pertuzumab subgroups, the results suggest a correlation between previous exposure to anthracyclines and radiotherapy, and subsequent development of TIC , which was expected. There was no significant association in development of pericarditis or thrombosis. Furthermore a negative ER/PR status was not a contributing risk factor in these sub-groups.
- There appears to be no significant difference in the cardiotoxicity profile in patients receiving both pertuzumab and trastuzumab as a combination therapy as compared to trastuzumab alone.
- Current practice in our centres is to measure LEVF every 3 months for the combination as per licensed recommendations of the UK Perjeta® SmPC. However we monitor LVEF 4 monthly for patients receiving trastuzumab as per recommendations in the Jones *et al.* 2009 UKNCRI position paper.
- There is an increased number of patients developing hypertension during therapy with HER-2 agents requiring a closer evaluation and monitoring to prevent risks of cardiomyopathy.
- Because no prospective randomized trials have ever been performed, patients with targeted therapies induced cardiomyopathies are not treated in a homogeneous manner, and no evidence-based recommendations for their management have been formulated.
- Close collaboration with a cardiologist team is required in order to draw up evidence and consensus based cardiac risk assessments using a traffic light system for establishing LEVF monitoring frequency, further cardiac assessment, referral pathways and recommendations for stopping and resuming HER-2 targeted therapies. This assessment must be built in the electronic patient platform ensuring auditability and automatic generation of referral letters.
- In the absence of risk factors an umbrella recommendation for trastuzumab +/- pertuzumab and TDM-1 patients, would be to monitor LVEF 4 monthly, based on the results of this study. This would be more economical and convenient for our HER2+ mBC patients.

References

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(2) **Cardiotoxicity of Trastuzumab** and other Her2-targeted agents, clinical uptodate.com
(3) **Cardiovascular toxicity associated with Trastuzumab therapy** : NICE appraisal
(4) **SmPC for Kadcyla, Herceptin and Perjeta via www.medicines.org.uk**