Research Article

PROSPECTIVE OBSERVATIONAL STUDY ON SAFETY AND EFFECTIVENESS OF TRASTUZUMAB IN HER- 2 POSITIVE BREAST CANCER PATIENTS

Trupthi B V[1], Venugopal B R[1], Jijo Joji[*2], Umera Sulthana[1], Vishweshwara M S[3], Hanumanthachar Joshi[4]

[1]Pharm D 5th year students, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

[2]Assistant Professor, Department of Pharmacy Practice, SVCP, Mysuru, Karnataka, India.

[3]Medical Superintendent, Senior Radiation Oncologist, Bharath Hospital and Institute of Oncology, Mysuru

[4]Principal, SaradaVilas College of Pharmacy, Mysore, Karnataka, India

*Corresponding Author: Dr Jijo Joji, Department of Pharmacy Practice, Sarada Vilas College of Pharmacy, Krishnamurthy Puram, Mysore-570004. Karnataka, India.

ABSTRACT:

Introduction: Targeting HER-2 receptor cells with the targeted medication trastuzumab, which inhibits the proliferation of cancer cells, is used clinically for HER-2-positive breast cancer patients. Although it is used to treat several other types of cancer, HER-2-positive breast cancer patients benefit more from it. The effectiveness and safety of trastuzumab are the main topics of the study. With few adverse events reported, this therapy is typically well tolerated.

Methods: A total of 35 HER-2 positive breast cancer patients with consent were enrolled, and their trastuzumab treatment was evaluated for its effectiveness and safety. Naranjo Causality Assessment Scale, Uppsala Monitoring Scales, Hartwig severity scale and Common Terminology Criteria for Adverse Event (CTCAE) questionnaires were used to assess its safety and effectiveness. With the aid of IBM SPSS, the outcomes will be documented.

Results: Patients who chose trastuzumab as either an adjuvant or neoadjuvant therapy for HER-2-positive breast cancer underwent a six-month follow-up. On average, the tumour size has decreased or shrunk in 34 out of 35 individuals. Only 19% of patients exhibited grade 1 or 2 (asymptomatic) LV impairment as a result of concomitant therapy, while 47% of patients had normal cardiac function. Infusion responses were more common, affecting 50% of the study population, and they were grade 1 during the first cycle of drug administration. Grade 2 neutropenia was observed in 3 patients. Grade 1 or 2 thrombocytopenia was caused by a reduced platelet count in 30% of individuals. 80% of the study's participants were leukaemia-free.

Conclusion: In our research population, the risk of disease progression or mortality was essentially non-existent among patients with HER-2-positive breast cancer who received trastuzumab. ADR occurred were of grade 1 and 2 which doesn't interfere with the normal quality of life. The tumour size decrease was observed in 97% of study population, which is significant proof that trastuzumab is a safe and efficient in treatment of HER-2 positive breast cancer.

INTRODUCTION:

Cancer is a broad class of disorders that can develop in, virtually any organ or body tissue. It can be stated simply that aberrant cells proliferate out of control until they infect neighbouring bodily sections beyond their natural boundaries. The term "cancer" is frequently used to refer to neoplasm and malignancy.

After skin cancer, breast cancer is the second most frequent malignancy among women. Men can occasionally also develop it. It is simply the tumour growth that takes place.

About 15%–20% of breast tumors contain higher amounts of receptors, which are known as Human Epidermal Growth Factor Receptor-2 (HER-2)

proteins. HER-2- 3 positive breast cancer is the type of breast cancer that tests positive for this protein. The regulation of the proliferation and repair of breast cells is carried out by these HER-2 proteins. Tumor cells multiply uncontrollably when these proteins are overexpressed. As a result, HER-2-positive cells are typically more aggressive than HER-2-negative cells.

The treatment options in general for HER-2-positive individuals include surgery, targeted therapy (HER-2-directed therapy), endocrine therapy, and radiation therapy. A combination of these therapies is also the choice of treatment which depends on the patient's condition.

Trastuzumab is the targeted therapy that binds to the HER-2 receptors and thereby decreases the overexpression of these proteins leading to no growth of tumor cells. Trastuzumab can be given as either adjuvant or neo-adjuvant therapy through an IV route. It may be given on a weekly schedule or once every 3 weeks. It can be combined with other drugs to improve the overall effect of the drug on the ER cells.

The main ADRs of trastuzumab include cardiomyopathy, infusion reactions, exacerbation of chemotherapy-induced neutropenia, and pulmonary toxicity. The ADRs include pain, asthenia, fever, chills, headache, abdominal pain, back pain, allergic reaction, anemia, leukopenia, neuropathy, rash, and so on.

MATERIALS AND METHOD:

Study site: The study was conducted at Bharath Hospital and Institute of Oncology (BHIO) Mysore.

Study design: The study was designed to be a prospective observational study. The sample size of the study was 35 patients.

Study period: The study was carried out for a period of six months.

Ethical approval: Institutional Human Ethical Committee of Bharath Hospital and Institute of Oncology (BIO), Mysore approved the study.

Study criteria:

Inclusion criteria:

1. Adult patients >/=18 years of age.
2. Patients diagnosed with HER-2-positive breast cancer.
3. Known hormone receptor status.
4. Patients receiving trastuzumab as their treatment regimen.

Exclusion criteria:

1. Treatment with any other anti-cancer investigational drug.
2. Pregnant or lactating women. 29
3. History of hypersensitivity reaction to trastuzumab or any components of products.
4. Patient is not willing to participate in the study.
5. Patients who are not adherent to treatment.

Source of data: All the relevant and necessary data will be collected from patient's case records, Patients interview, Prescriptions of patients, Interviewing healthcare professionals, CTCAE questionnaire, Data collection form, Any other relevant sources.

Study procedure: The study involved the following steps: -

1. Preparation of informed consent form (ICF): An informed consent form was suitably designed both in English (Annexure 1) as well as in Kannada (Annexure 2) to obtain consent from patients who volunteered for the study and fulfilled the study criteria. The ICF was reviewed and approved by the institutional ethics committee. The patient was explained about the study and consent was obtained after they voluntarily agreed after being aware of every important aspect regarding the study. For those patients who were illiterate, the study was discussed with them, and consent was obtained from caretakers.

2. Preparation of data collection form (DCF): A specially designed data collection form (Annexure 3) was designed for the study. The particulars included demographic details like name, age, gender, family history, social habits (smoking, tobacco chewing, and alcoholism), diet, weight, height, and body surface area. Clinical data such as diagnosis, past medical history, past medication history, allergy status, staging of cancer, and TNM classification. Therapeutic data such as the name of the drug, dose, frequency, duration, route of administration, details on the supportive medication 30 used, premedication, and discharge medications. It also contains the details of laboratory test results and other tests like biopsy reports, PET CT scan reports, and 2D ECHO reports to interpret the outcome of the drug. To assess the ADR of a drug, Common Terminology Criteria for Adverse Event (CTCAE) questionnaires, Naranjo Causality Assessment Scale, Hartwig severity scale and Uppsala monitoring scales were included. The same details will be documented using IBM SPSS Statistics version 22.

3. Patient enrollment: Patients fulfilling the study criteria were enrolled in the study after obtaining informed consent. Patients were enrolled in in-patient general wards, private wards, and daycare centers which are even covered under

governmental schemes.

4. Data collection: All relevant details of the enrolled patients were obtained from various data sources and documented in the data collection form.

5. Assessment of safety and efficacy of drug in breast cancer patients: The drug effectiveness was evaluated from laboratory data before and after the drug was administered. And tumor size was checked before and after treatment to obtain the results of effective treatment. The drug safety was evaluated from grading ADR that had occurred in the study subjects. The patients ADR were assessed three grading criteria, CTCAE grading, WHOUMC causality assessment criteria, NARANJO adverse drug reaction probability scale.

a) CTCAE grading: The ADR were graded based on CTCAE criteria; the grading is given 1 to 4.

b) NARANJO adverse drug reaction probability scale: The Naranjo ADR probability scale was developed to help standardize assessment of causality for all adverse drug reactions. The scale was also designed for use in controlled 31 trials and registration studies of new medications, rather than in routine clinical practice. The scoring is categorized as, Doubtful,Possible, Probable, Definite.

c) WHO-UMC causality assessment criteria: in this method it gives guidance to the general arguments which should be used to select one category over another. The various causality categories and the assessment criteria of the various categories are: Certain, Probable / likely, Possible, Unlikely, Conditional / Unclassified, Unassessable/ Unclassifiable.

Statistical analysis: A descriptive statistic was presented in terms of frequency and percentages for categorical value. Mean, Standard deviation was used to describe the general characteristics of the study sample. An inferential statistic will be done by using Spearman correlation and Wilcoxon signed-rank test with the help of IBM SPSS Version 22, to determine the linear correlation between the variables and the outcome results were interpreted according to the degree of association as: Strong (rs = ±0.5 to 1.0), moderate (rs = ±0.3 to 0.49), weak (rs = ±0.1 to 0.29) and very weak (rs = ±0.9 to 0) after taking significant correlation ($p < 0.01$ or $p < 0.05$) values into considerations.

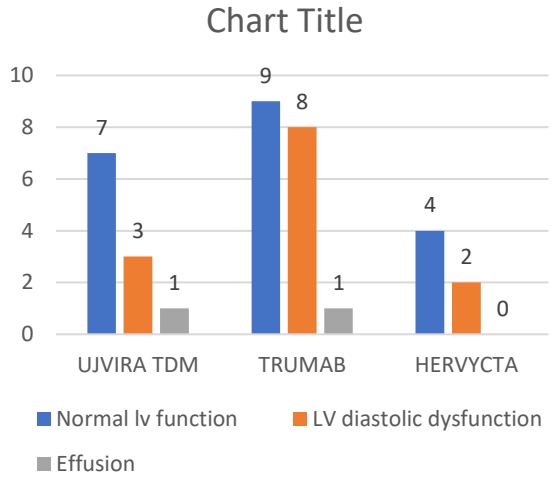
RESULTS:

There were total of 3 different types of trastuzumab used in the study population. Those were namely UJVIRA TDM1 from Zydus Cadila with price range of Rs. 32495 for a 100mg vial. TRUMAB from Glenmark with price range of Rs. 63233 for 440mg vial. HERVYCTA from Dr Reddy's Laboratories Ltd. with price range of Rs. 62497 for a 440mg vial.

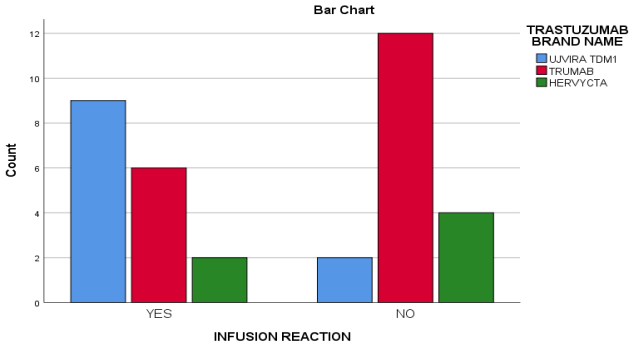
Assessment of safety and efficacy of trastuzumab in her-2 positive breast cancer

The main ADE to be monitored during administration of trastuzumab drug was cardiac monitoring by 2D ECHO test, infusion reaction, anemia, neutropenia and alopecia.

Cardiac events: One of the most common side effects of trastuzumab treatment is cardiotoxicity manifested as heart failure, accompanied by a decrease in left ventricular ejection fraction (LVEF) or an asymptomatic decrease in LVEF.



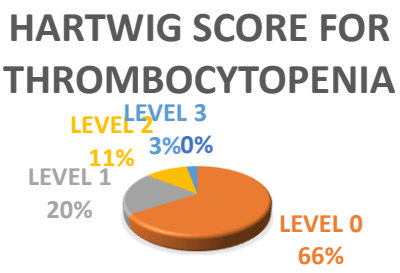
Infusion reaction: Infusion reaction is the common ADR exhibited by trastuzumab. The most common symptoms include fever, chills, breathlessness, and rashes in the body. The reaction occurs immediately after uptake of trastuzumab to body.



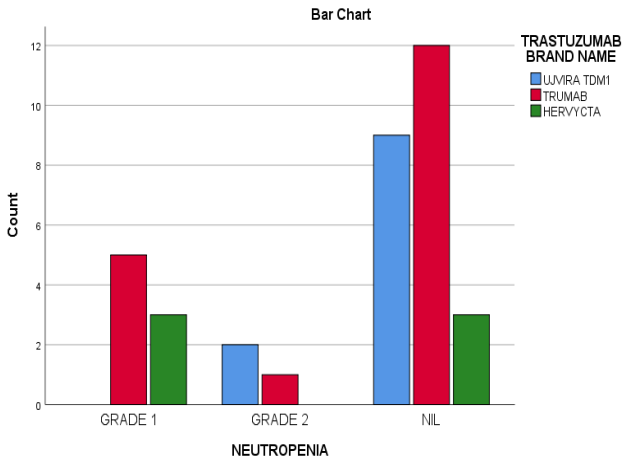
Majority of patients exhibit the symptoms of infusion reaction as a result of anaphylactic reaction after 1st dose of drug consumption. In this study we found 50% chance of occurrence of this reaction. In our study Hartwig scoring for severity was conducted and observed that the severity were of level 1, which explicit that infusion reactions occurred were subsided after administration of hydrocortisone and bring back patients to normal condition.

THROMBOCYTOPENIA: 31% of the patients receiving trastuzumab had experienced decrease platelet count. And remaining 68% had normal platelet count.

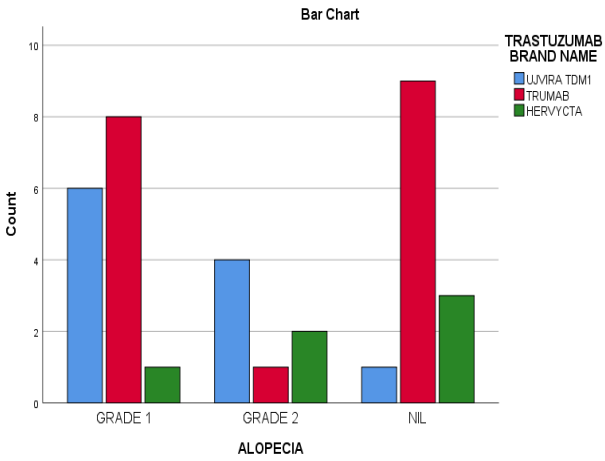
Thrombocytopenia due to trastuzumab was found in few patients. 6 patients out of 11 who received ujvira had grade 1 and 2 thrombocytopenia. 4 out of 18 patients had grade 1 and 2 40 thrombocytopenia in patients receiving trumab. whereas 2 patients on hervycta had grade 3 thrombocytopenia.



Neutropenia: Chemotherapy induced neutropenia (CIN) is a major cause of hematological and doselimiting toxicities of chemotherapy.it may have short- or long-term impacts on treatment plans which may result in unfavorable disease survival. 17 out of 35 patients had normal neutrophil count (48%). 13 patients had complaints of decreased neutrophil count.

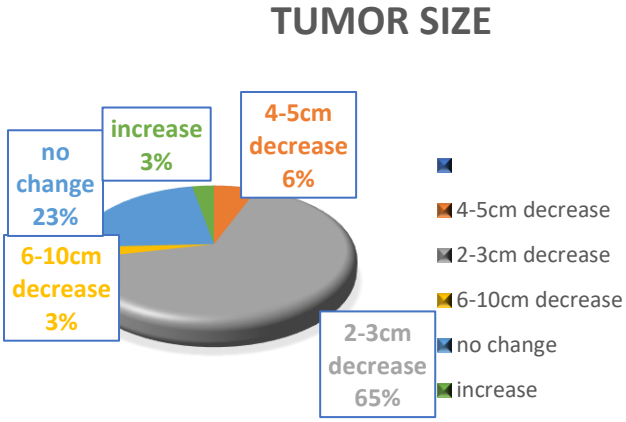


Alopecia: Alopecia is one of the most common complaints from the patients who received chemotherapy. Drug induced alopecia is common in cytotoxic drugs, as a result it sets a benchmark identification for receiving chemotherapy. Only 20 % of the population had complaints of grade 2 hair loss as a result of trastuzumab therapy.

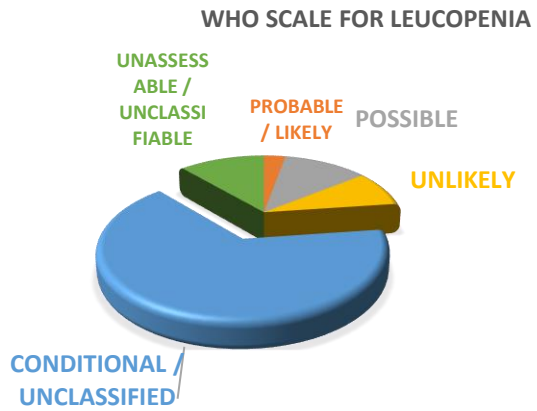


Tumor size: Tumor size is the most important factor for assessing the efficacy of drug. Patients are advised to have a PET Scan after every 4 cycles of the treatment, this enables the physician to determine the treatment success rate. In most of the patients we found decrease in the tumor size, whereas few patients couldn't undergo PET scan due to financial scarcity which resulted in deprivation of knowledge about tumor size.

In our study only 20 % of the population had complaints of grade 2 hair loss as a result of trastuzumab therapy.



Leucopenia: Leukemia is the common condition exhibited in cancer patients. Leukemia is the cancer of blood forming tissues, including bone marrow. Leukemia free state can be considered as one of the factors to determine drug efficiency.8 of them experienced low WBC count



CONCLUSION:

Targeted therapy is a main choice of therapy for HER2 positive breast cancer patients. There were 3 brands of trastuzumab that currently used in Bharath Cancer Hospital namely, UJVIRA TDM1 from Zydus Cadila, TRUMAB from Glenmark, and HERVYCTA from Dr Reddy's Laboratories Ltd. 35 patients receiving trastuzumab for HER2 positive breast cancer were included in our study.

We found that exposure to trastuzumab had remarkable reduction in tumor size except for 1 patient who had progressed the disease to have metastasis. Trumab exhibited more percentage decrease than other 2 drugs. Majority of patients had normal neutrophil count, but 36% of them exhibited decreased neutrophil count which were of grade 1 and 2. There was no evidence for grade 3 neutropenia which suggest the effectiveness of trastuzumab. 68% of patient receiving trastuzumab had normal platelet count, remaining patients had grade 1 and 2 decrease in platelet count. Among which trumab had higher percentage of patients with normal count. Among 74% of patients' leukemia free state was observed which makes that trastuzumab usage is safe and effective.

Monitoring cardiac events to identify decrease in LVEF which suggest possible cardiac dysfunction. Here in our study grade 1 LV diastolic dysfunction was majorly found in patients receiving trumab as their treatment choice. Infusion reaction is the common ADRs that are reported in other studies. In our study 50% of patients had observed infusion reaction on their first dose of drug, which was relieved after 1 or 2 hrs. of stopping drug infusion. There is no major decrease in neutrophil and platelet count which symbolizes the safe usage of treatment drug. Alopecia is quite commonly observed in patients who are under chemotherapy. On use of trastuzumab only 20% had complaints of grade 2 hair loss.

Since there were no major evidence of ADR incidence in the study population, we can conclude that usage of trastuzumab was safe and effective. Among all 3 different drug trumab had promising effect than other 2 drugs.

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