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Indian Journal of Physiology and Pharmacology

Review Article

Comparison of adverse effects of trastuzumab with other drug combinations for the treatment of breast cancer: A review

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Received : 25 October 2021
Accepted : 20 April 2022
Published : 31 May 2022

DOI
10.25259/IJPP_390_2021

Quick Response Code:

ABSTRACT

Objectives: This study compares the adverse effects (AEs) associated with trastuzumab in the treatment of human epidermal growth factor receptor 2-positive breast cancer (HER-2 + BC) when used alone or in combination with chemotherapy or with tyrosine kinase inhibitors, so as to aid in rational treatment choices.

Materials and Methods: An electronic search was conducted on PubMed using the Mesh terms 'BC', 'HER-2 positive', 'metastasis BC, 'trastuzumab', and 'safety'. Data from 32 studies regarding AEs were extracted and categorised as trastuzumab + chemotherapy (T+C), trastuzumab biosimilar (Tb), trastuzumab + tyrosine kinase inhibitors+ chemotherapy (T+TKi+C), and trastuzumab + tyrosine kinase inhibitors (T+TKi). The data are presented as the mean percentage of AEs. The statistical comparison was represented by a box and whisker plot of the interquartile range value of AEs.

Results: AEs related to the gastrointestinal tract, skin, nervous, blood, and lymph were reported to be the most common in T+C, T+TKi+C, and T+TKi. Nausea, vomiting, diarrhoea, constipation, neuropathy peripheral, alopecia, rash, anaemia, leucopenia, raised aspartate transaminase and alanine transaminase were the most common complaints. AEs such as myalgia, nasopharyngitis, hypertension, and ejection fraction decrease was reported to be the most common in Tb.

Conclusion: This study concluded that biosimilar of trastuzumab is safest for the treatment of HER-2-positive BC. Cardiovascular disorder is often reported in the biosimilar group, but this group has fewer AEs reported as compared with chemotherapy, and tyrosine kinase inhibitors groups related to other systems such as digestive, nervous, and respiratory. The choice of combination is depending on the type of BC and the condition of the patients. The patients must monitor for cardiotoxicity when the biosimilar of trastuzumab is used.

Keywords: Adverse effects, Trastuzumab, Tyrosine kinase inhibitor, HER-2-positive, Metastatic breast cancer

INTRODUCTION

Breast cancer (BC) is the most common cancer among women.[1] In 2017, more than 250,000 new cases of BC were discovered in the United States, and it is estimated that 12% of all women in the US will be diagnosed with BC at some point in their lives. About 62% of BC are restricted to the breast at the time of diagnosis, while another 31% have progressed to lymph nodes around the breast.[2] The BC accounts for 14% of all cancers in Indian women. One woman gets diagnosed with BC every

4 min in India and one woman dies of BC every 13 min, making it the most prevalent cancer among women.[3] In 2018, about 162,468 new registered cases of BC and 87,090 deaths were recorded in the country. By 2030, BC is expected to cause more deaths among women in India than any other cancer.[4]

HER-2 is a tyrosine kinase receptor that facilitates signalling pathways of cell growth, division, motility, and repair in normal cells.[5] Overexpression of HER-2 activates the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) 'survival pathway' whose action favours cell proliferation apparently by inhibiting apoptosis.[6] The 'survival' signal is normally coupled to the activation of the mitogenic signal involving mitogen-activated protein kinases (MAPK) pathway recruitment. Increased HER-2 expression in cancer enhances and prolongs signalling from both the PI3K/Akt and MAPK pathways, associating upregulation of HER-2 to the BC.[7]

Patients with HER-2 Positive BC are given treatment before surgery to reduce the tumor size and the neoadjuvant therapy after surgery to prevent the reoccurance of BC. Various treatments for these are chemotherapy,target therapy like tyrosine kinase inhibitors , hormonal therapy like PI3K/Akt/mTOR inhibitors (everolimus), CDK4/6 inhibitors, antiPD(L)1(programmed cell death protein ligand 1) antibodies, endocrine therapy.[8] The treatment is recommended to start within 2–6 weeks after the surgery.[9]

Trastuzumab is a recombinant humanised IgG_1 monoclonal antibody against the extracellular domain of the HER-2 receptor (ErbB-2). The HER-2 receptor consists of an extracellular ligand-binding domain, a transmembrane region, and an intracellular or cytoplasmic tyrosine kinase domain. Trastuzumab binds to the extracellular domain of HER-2 and prevents cleavage of the extracellular domain of HER-2 and thereby activation of the receptor; blocking the dimerization of HER-2. By binding to the juxta membrane domain of HER-2, trastuzumab triggers the downregulation of HER-2 expression.[10] It may be administered by a 3-week cycle (i.e., the initial dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks) or by a weekly cycle (i.e., initial dose of 4 mg/kg, followed by 51 further weekly doses of 2 mg/kg) and sequentially or concurrently with standard chemotherapy of anthracycline-taxane regimens (e.g., doxorubicin and cyclophosphamide [AC] plus paclitaxel/docetaxel or fluorouracil, epirubicin and cyclophosphamide plus docetaxel/paclitaxel), taxane regimen (e.g., docetaxel plus cyclophosphamide) or anthracycline regimen (e.g., AC). Trastuzumab is currently available as 150 mg (single-dose vial) and 440 mg (multidose vial) powder for concentrate solution for intravenous infusion and for subcutaneous injection containing 600 mg/5 mL. Most often, combinations of 2 or 3 of these drugs are used as adjuvant or neoadjuvant therapy.[11]

There are scattered reports of adverse effects (AEs) with trastuzumab or chemotherapy with or without tyrosine kinase inhibitors and a comparative analysis of the safety of trastuzumab with the different treatment regimens is not available. This is essential as it can assist clinicians to make the rational treatment choice that can improve the quality of life and safety of the patient. Hence, to address this, we have compared the safety profile of chemotherapy drugs and TKi with trastuzumab in a single study present in this systematic review and meta-analysis.

MATERIALS AND METHODS

Search strategy

A literature search of databases was conducted on PubMed using MeSH terms 'BC', 'HER-2 positive', 'metastasis BC', 'adjuvant', 'neoadjuvant', 'trastuzumab', 'efficacy', and 'safety' from the first available year until December 2020. The websites of the American and European societies were searched for BC meetings for relevant presentations, abstracts, and references to related reviews. Only human studies in English were evaluated, as well as randomised control trials (RCTs), observational studies, and clinical trials.

Inclusion criteria

We had included all the studies of Phases-I, II, III, and IV RCTs of HER-2-positive BC in which Tb and trastuzumab were used with and without chemotherapy and TKi.

Exclusion criteria

The following were the criteria for exclusion**:** Review articles, articles without relevant data (study protocol article, diseases other than BC, a study conducted in healthy subjects and without access), and studies of experimental monoclonal antibodies (mAbs).

Data extraction

The following data were extracted from each study on Microsoft Excel: The first author's name, publication year, study design, number of patients, receptor status, trastuzumab dosage, chemotherapy regimen, mean age, stage, country, and AEs.

The studies which are included in this meta-analysis are categorised into six different categories as follows:

S. No.	Category	Number of studies
1.	Trastuzumab + chemotherapy	11
2.	Trastuzumab biosimilar	8
3.	Trastuzumab + chemotherapy + tyrosine kinase inhibitors	4
4.	Trastuzumab + tyrosine kinase inhibitors	9

Statistics

The data are presented as the mean percentage of AEs. The statistical comparison was done using GraphPad Prism version 8.4.2. The interquartile range (IQR) is presented in a box and whisker plot, plotted between % of AEs versus drug therapy.

Study selection flow

There were 275 articles found in the PubMed database after an electronic search. Their titles and abstracts were carefully examined and 207 were eliminated based on the methodology section's exclusion criteria. The whole text of the remaining 68 papers was reviewed for eligibility, while 43 were excluded due to the usage of trastuzumab in combination with other mAbs. Finally, 32 studies were included in this meta-analysis which was grouped [Figure 1].

RESULTS

Characteristics of studies

Most of the selected articles were published in the years 2016, 2017, and 2019 and belonged to Phases II and III of clinical trials. Most of the studies were multinational or conducted in the United States. The sponsors and partners in six research have not been revealed. One of the 32 studies was funded by a government body, while the rest were funded by private organisations.

Demographics and disease characteristics

The included 32 studies had a total of 12107 patients. Most of the studies are related to metastatic BC and HER2 + Stages II and III. Some of the patients were of followed up patients with ages between 30 and 80 years. The patient received trastuzumab with chemotherapy(n = 4500), or trastuzumab biosimilar (2417), or trastuzumab with tyrosine kinase inhibitors and chemotherapy (n = 719) or trastuzumab with tyrosine kinase inhibitors (n = 4471). The baseline characters of all the studies are shown [Table 1].[12-43]

AEs

The reported AEs from each of the groups were categorised according to the system organ class (SOC). The reported AEs were subcategorised such as nausea, vomiting, thrombocytopenia, pharyngitis, nasopharyngitis, headache, hypertension, raised alanine transaminase (ALT), or aspartate transaminase (AST), and injection site reaction.

General disorders and administration site conditions

Fatigue, asthenia, peripheral oedema, pyrexia, and mucosal inflammation were the most common general disorders.

The mean percentage of patients that reported general disorders and administration site conditions are mentioned [Table 2]. The IQR is shown [Figures 2a-d].

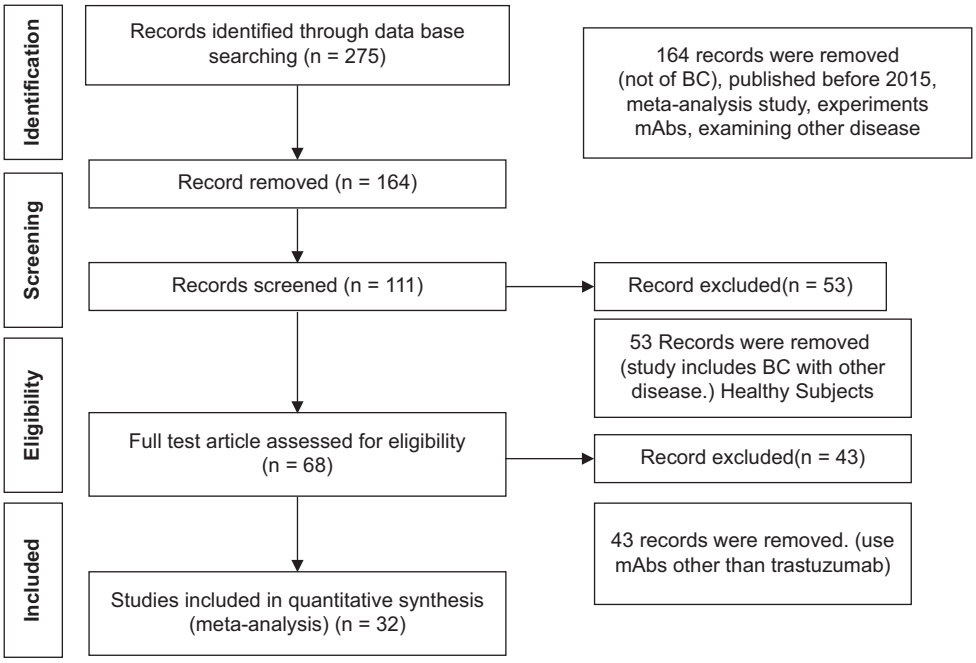

Figure 1: Flowchart of study.

Table 1: Overview of studies in each category study.

Disease stage	Number of patient (*n*)	Pre-menopausal patient (%)	Post-menopausal patients (%)	ER/PR receptor		Mean age (Years)
				Positive patients (%)	Negative patients (%)	
T+C						
HER-2 + Stages I–III invasive	50	38	62	50	50	58
HER-2 + primary BC	50	68.0	40.0	NA	NA	50
HER-2 + advanced BC	719	NA	NA	44.8	56.6	53.0
HER-2 + MBC trastuzumab resistant	59	NA	35	7	2	52
Metastatic or locally advanced HER-2-positive BC	26	23.1	69.2	NA	NA	50.7
HER-2 + early or locally advanced BC	30	NA	NA	56.7	43.3	48
Stage II or III HER-2 + BC	109	50	50	44	56	40
Phase III randomised short-HER study	1254	36	64	68	32	55
HER-2 + early BC	2174	33	67	66	66	56
HER-2 + operable BC	29	58.6	41.4	48.3	51.7	56
Tb						
HER-2 + BC	379	49.5		61.7	13.6	56.5
Pre-treated HER-2 + locally recurrent or MBC	73	NA		53	47	58
Stages I–IIIA operable HE-R+ BC	271	NA		57	43	51.8
HER-2 + early BC	1510	NA		NA	NA	53
Previously treated HER-2 + BC	184	954.1		37.0	32.8	55
T+TKi+C						
HER-2 + MBC	474	42	58	66.5	33.3	52
HER-2+ BC	245	NA	NA	50	59	55
T+TKi						
HER-2 + MBC	1646	47	53	29.22	20.77	52
HER-2 + unresectable, locally advanced or MBC	496	NA	NA	53	45	53
HER-2+ BC	69	NA	NA	39	60	55.5
HER-2 + MBC patients previously treated	115	63.5)	36.5	NA	NA	59.8

NA: Not available, ER: Oestrogen, PR: Progestogen, BC: Breast cancer, MBC: Metastatic breast cancer, F: Women, HER-2: Human epidermal growth factor receptor-2, T+C: Trastuzumab + chemotherapy, Tb: Trastuzumab biosimilar, T+TKi+C: Trastuzumab + tyrosine kinase inhibitors+ chemotherapy, T+TKi: Trastuzumab + tyrosine kinase inhibitors

Skin and subcutaneous tissue disorders

Alopecia, rash, nail disorder pruritus, palmar-plantar erythrodysesthesia, dry skin, and skin discolouration were the most common skin disorders.

The mean percentage of patients that reported skin and subcutaneous tissue disorders are mentioned [Table 2]. The IQR is shown [Figures 3a-e].

Gastrointestinal disorders

Diarrhoea, nausea, vomiting, constipation, anorexia, and abdominal pain were the most common GI disorders.

The mean percentage of patients that reported gastrointestinal disorders are mentioned [Table 2]. The IQR is shown [Figures 4a-h].

Nervous system disorders

Headache, neuropathy peripheral, peripheral sensory neuropathy, sensory neuropathy, and dizziness were the most common reported nervous system disorders.

The mean percentage of patients that reported nervous system disorders are mentioned [Table 2]. The IQR is shown [Figures 5a-d].

Table 2: Mean % of patient reporting AEs.

Mean% of patients	T+C	Tb	T+TKi+C	T+TKi
General disorders and administration site conditions				
Fatigue	18.65	11.08	34.2	28.18
Asthenia	12.3	1.1125	0	2
Pyrexia	3.61	4.5	2.95	2.22
Peripheral oedema	2.6	0	5.875	0
Skin and subcutaneous tissue disorders				
Alopecia	25.19	8.0125	6.025	15.37
Rash	13.58	2.9	11.225	7.11
Pruritus	5.07	0	2.95	0
Palmar-plantar erythrodysesthesia	1.2	0	16.175	1.22
Gastrointestinal disorders				
Diarrhoea	9.1	43.2	29.21	42.05
Nausea	18.73	25.44	28.61	26.675
Vomiting	12.22	12.26	15.45	8.825
Constipation	8.57	3.11	10.61	6.175
Stomatitis	2	2.33	8.18	7.35
Abdominal pain	2.1	2.97	0.97	2.95
Anorexia	4.16	1.58	10	4.3
Dyspepsia	0	0	2.11	4.4
Oral mucositis	0	0	1.98	6.9
Abdominal pain upper	2.1	2.97	0.97	2.95
Nervous system disorders				
Headache	3.9	6.91	7.44	2.95
Neuropathy peripheral	9.93	0	8.43	0
Peripheral sensory neuropathy	12.85	3.46	3.17	0
Dizziness	1.71	0	2.44	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	0	0	1.22	2.95
Pain in extremity	1.06	0	2.33	0
Arthralgia	8.57	0	10.3	0
Myalgia	7.99	33.3	4.86	0
Back pain	1.01	0	1.66	0
Infections and infestations				
Paronychia	0	0	13.57	3.44
UTI	0	0	5.87	1.64
Injection site pain	0	0	0	0
Upper respiratory tract infection	0	0	1.47	1.33
Nasopharyngitis	4.12	1.11	2.45	0
Infusion-related reaction	2.76	0.4	1.45	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	11.375	2.77	2.64	7.9
Cough	5.83	3.11	6.2	2.95
Metabolism and nutrition disorders				
Decreased appetite	5.58	7.625	5.66	8.82
Hypokalaemia	0	6.25	1.58	8.82
Hyponatremia	0	0	0.53	3.45
Hypocalcaemia	0	0	0.53	1.72
Eye disorders				
Dry eye	0	0	4.4	0
Psychiatric disorders				
Depression	3.81	0	1.775	0
Insomnia	2.9	0	0	1.55
Anxiety	3.81	0	0	0
Blood and lymphatic system disorders				
Anaemia	5.92	13.25	33.77	11.2

(Contd...)

Table 2: *(Continued).*

Mean% of patients	T+C	Tb	T+TKi+C	T+TKi
Leucopenia	0.32	9.75	6.79	10.37
Neutropenia	7.6	14.54	27.47	16.75
Thrombocytopenia	10.18	4.38	12.06	0
Investigational disorder				
Raised AST	8.96	13.81	17.25	25.45
Increase WBC	6.81	1.64	0	0
Raised ALT	5.97	9.87	17.6	28.32
ALP increased	1.81	0	9	1
Blood bilirubin increased	8.33	1.08	0	1.51
Increase neutrophil count	1.99	0	1.77	0
Cardiovascular disorders				
Cardiac disorder	2.38	1.14	0	0
LSVD increase	0.42	0.48	0	0
Congestive heart failure	0	0	0	0
Left ventricular dysfunction	0	0	0	0
Palpitation	0	0	0	0
Hypertension	0.375	1.01	0	0
Hot flush	0	0	0	0
Palpitations	0	0	0	0
Reference	12–22	23–30	31–34	35–41

n: Total patients, LSVD: Left ventricle systolic dysfunction, UTI: Urinary tract infection, AST: Aspartate transaminase, ALT: Alanine transaminase, WBC: White blood cell, AEs: Adverse effects

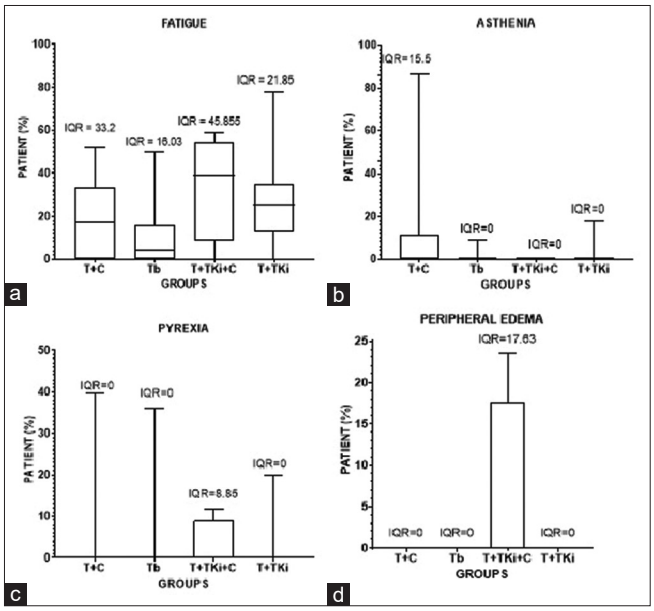

Figure 2: Box and whisker representation of the range of patients in different groups showing (a) fatigue, (b) asthenia, (c) pyrexia and (d) peripheral oedema.

Musculoskeletal and connective tissue disorders

Muscle spasms, pain in the extremity, arthralgia, and myalgia were the most common musculoskeletal and connective tissue disorders.

The mean percentage of patients that reported musculoskeletal and connective tissue disorders are mentioned [Table 2]. The IQR is shown [Figures 6a-d].

Infections and infestations disorder

Paronychia, urinary tract infection, injection site pain, upper respiratory tract infection, nasopharyngitis, and infusion-related reaction were the most common infections and infestations disorders.

The mean percentage of patients that reported infections and infestations disorders are mentioned [Table 2]. The IQR is shown [Figures 7a-d].

Respiratory, thoracic, and mediastinal disorders

Dyspnoea, epistaxis, and cough were the most common respiratory, thoracic and mediastinal disorders.

The mean percentage of patients that reported respiratory, thoracic, and mediastinal disorders are mentioned [Table 2]. The IQR is shown [Figures 8a-c].

Metabolism and nutrition disorders

Decreased, hypokalaemia, hyponatremia, hypocalcaemia, and hypomagnesaemia were the most common metabolism and nutrition disorders.

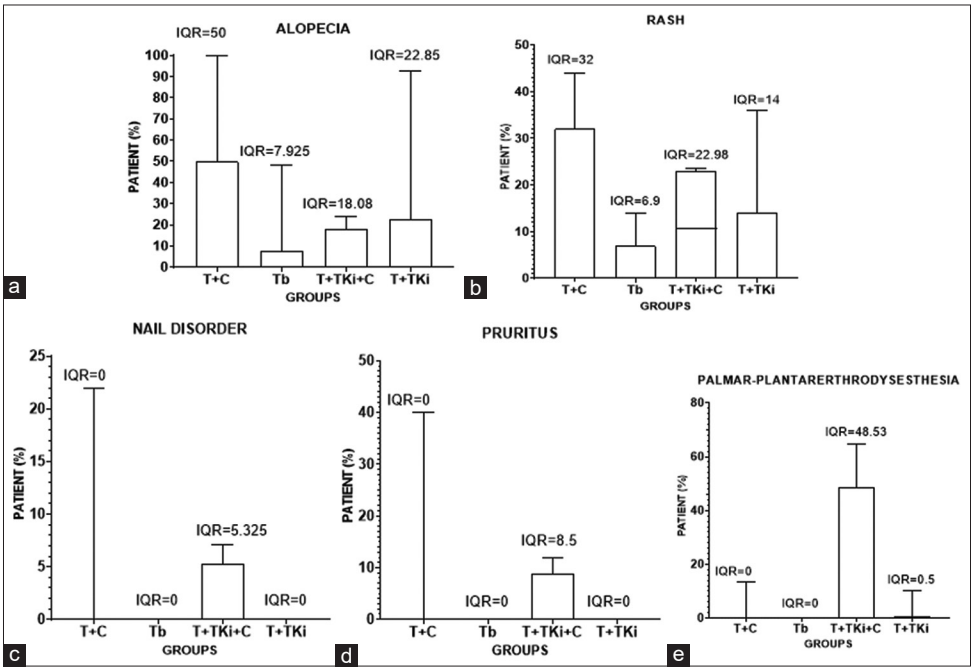

Figure 3: Box and whisker representation of the range of patients in different groups showing (a) fatigue, (b) asthenia, (c) pyrexia, (d) peripheral oedema and (e) palmar-plantar erythrodysesthesia.

The mean percentage of patients that reported metabolism and nutrition disorders are mentioned [Table 2]. The IQR is shown [Figures 9a-d].

Eye disorders

Dry eye was a common eye disorder.

The mean percentage of patients that reported these eye disorders are mentioned [Table 2]. The IQR is shown [Figure 10].

Psychiatric disorders

Depression and insomnia anxiety were the most common psychiatric disorders. The mean percentage of patients that reported psychiatric disorders are mentioned [Table 2]. The IQR is shown [Figure 11].

Blood and lymphatic system disorders

Anaemia, leucopenia, neutropenia, and thrombocytopaenia were the most common blood and lymphatic system disorders.

The mean percentage of patients that reported blood and lymphatic system disorders are mentioned [Table 2]. The IQR is shown [Figures 12a-d].

Investigational disorders

Raised AST, ALT, increase WBC, and decreased platelet count were the most common investigational disorders.

The mean percentage of patients that reported investigational disorders are mentioned [Table 2]. The IQR is shown [Figures 13a-c].

Cardiovascular disorders

The mean percentage of patients that reported cardiac disorder, ejection fraction decrease, and palpitation left ventricular dysfunction were the most common cardiovascular disorders. No vascular disorder was reported in T+TKi+C and T+TKi.

The mean percentage of patients that reported investigational disorders are mentioned [Table 2]. The IQR is shown [Figures 14a and b].

Mortality

In most of the studies, no deaths were reported due to monoclonal antibody-associated AEs. The reasons behind these deaths include congestive heart failure, left ventricular systolic dysfunction, BC, or any other reasons which were not specified.

DISCUSSION

The term BC refers to a malignant tumour that has developed from cells in the breast. Usually, BC either begins in the cells of the lobules, which are the milk-producing glands, or the ducts, the passages that drain milk from the lobules to the nipple. The treatment plans for BC are usually classified

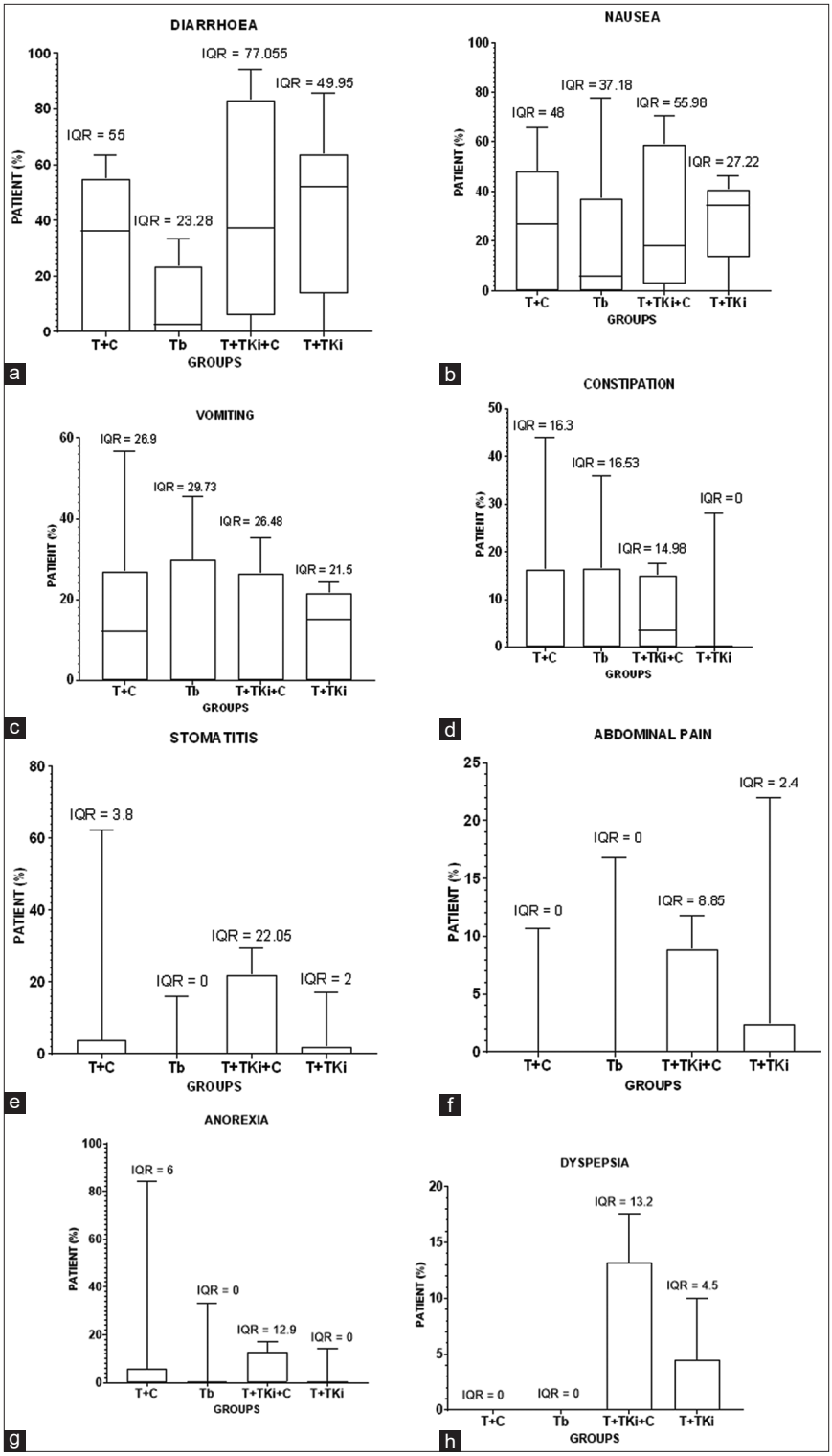

Figure 4: (a and b) Box and whisker representation of the range of patients in different groups showing (a) diarrhoea, (b) nausea, (c) vomiting, (d) constipation, (e) stomatitis, (f) abdominal pain, (g) anorexia and (h) dyspepsia.

according to the type of disease, its stage, and any special circumstances. Some treatments are local, which means that they only impact the tumour and not the rest of the body. Most of the women with BC will undergo surgery to remove the tumour. The first-line treatment option for HER-2-positive BC is a combination of pertuzumab, trastuzumab,

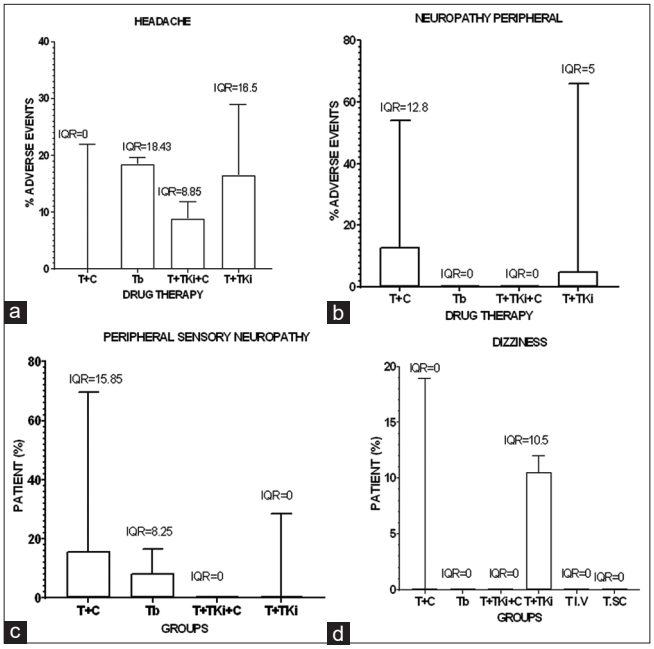

Figure 5: Box and whisker representation of the range of patients in different groups showing (a) headache, (b) peripheral neuropathy, (c) peripheral sensory neuropathy and (d) dizziness.

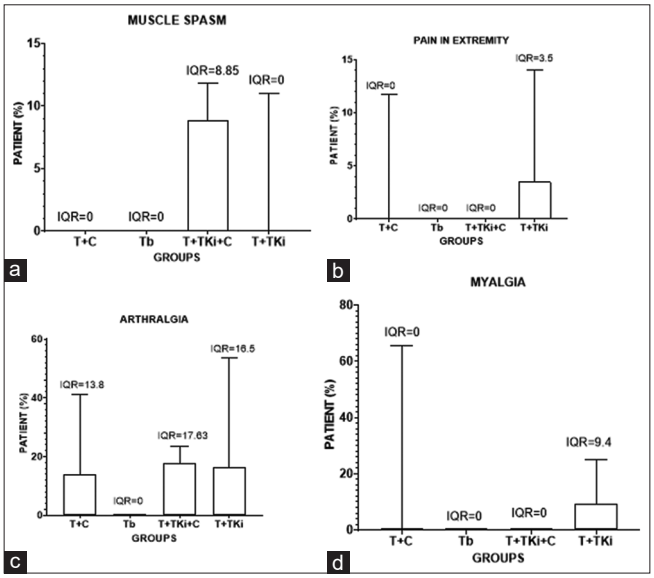

Figure 6: Box and whisker representation of the range of patients in different groups showing (a) muscle and spasm, (b) pain in extremity, (c) arthralgia and (d) myalgia.

and a single chemotherapeutic drug.[44] In the second-line treatment, monotherapy of trastuzumab emtansine (T-DM1) is used which is an antibody-drug conjugate that incorporates the HER2-targeted anti-tumour properties of trastuzumab with the cytotoxic activity of the microtubule inhibitory agent (a derivative of maytansine [DM1]) and allows intracellular drug delivery specifically to HER2-overexpressing cells.[45] Beyond trastuzumab, pertuzumab, and T-DM1, a new class of therapy that is, tyrosine kinase inhibitors (neratinib and tucatinib), were approved for the treatment of HER-2-positive BC that had progressed despite routine treatment after trastuzumab. Bottom of FormOther emerging therapies and novel combinations Top of Form Bottom of Formsuch as the immune checkpoint inhibitors (Keytruda), CDK4/6 inhibitors, and alpha-specific PI3K inhibitors (alpelisib) were also approved.[46]

Trastuzumab therapy prolongs the survival of patients with HER-2 BC when combined with chemotherapy or with tyrosine kinase inhibitors and has been demonstrated to lead a dramatic improvements in disease-free survival.Trastuzumab is a specially made antibody that targets HER-2-positive cancer cells. Trastuzumab attaches to the HER-2 protein on the surface of HER-2-positive cancer cells. Data suggested that both dual HER-2 blockades and mono HER-2 blockade increase AEs risk and huge differences were found among the treatment strategy subgroups.[47]

In the absence of head-to-head to trial, we have conducted a meta-analysis of various study (original research) articles published during the year from 2016 to 2020. The research was done on 27 January 2021. We found 275 articles on PubMed out of which 111 were screening for analyses. Out of 111, we included 35 articles for our study. Out of 32 studies, maximum studies were of Phases II and III CT, conducted in 2017–2019 on age group 71–80 and mainly conducted in the USA. Our main concern or main objective is to study adverse events.

The reported AEs from each of the groups were categorised according to the SOC. The maximum number of AEs reported are related to digestive after that blood-related disorder. The five most prevalent general disorders were noted, with fatigue and asthenia being the most common. The T+C regimen and T+TKi+C regimen had the largest percentage of subjects reporting overall disorder, while the Tb had the lowest rate. Moreover, percentages, respectively, indicating that overall disorder was prevalent in the T+C and T+TKi+C groups. The four most prevalent skin disorders were identified, with baldness and rash being the most common. The T+C regimen had the largest percentage of subjects reporting skin disorder and the T+TKi+C regimen had the lowest percentage. The 13 most frequent digestive system disorders were reported, including diarrhoea, nausea, vomiting, constipation, stomatitis, anorexia, and stomach pain. The T+TKi+C regimen had the largest percentage of subjects reporting digestive disorders. The five most prevalent nerve system disorders were documented, with headaches and neuropathy being the most common. T+C regimens had the largest percentage of subjects reporting neurological disorders followed by T+TKi+C regimens. In the musculoskeletal system, disorder arthralgia, pain in extremity, and back pain in the most common were reported.

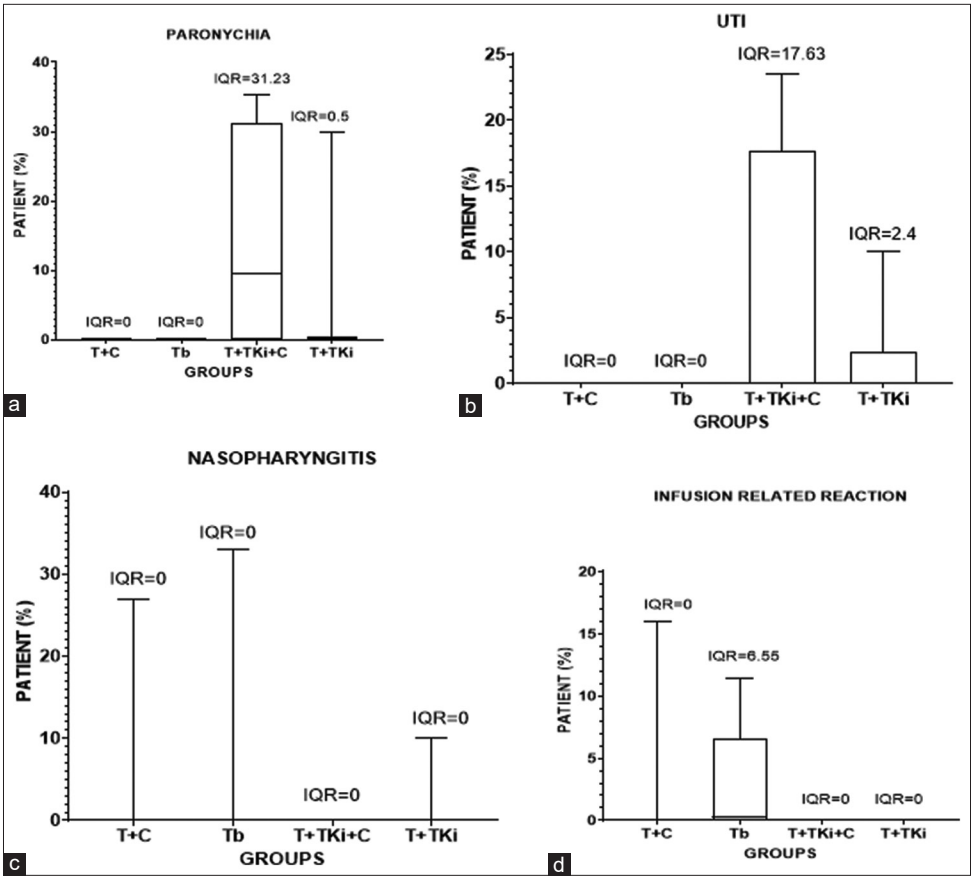

Figure 7: Box and whisker representation of the range of patients in different groups showing (a) paronychia, (b) UTI, (d) nasopharyngitis and (d) infusion-related reaction.

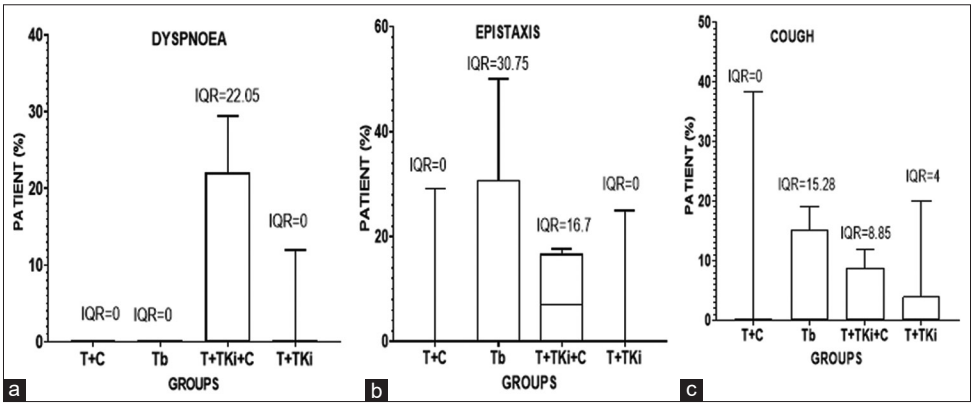

Figure 8: Box and whisker representation of the range of patients in different groups showing (a) dyspnoea, (b) epistaxis and (c) cough.

The highest percentage in subject reported musculoskeletal system disorder were of T+TKi+C and T+C regimen. In respiratory system, disorder cough and epistaxis were most commonly reported. The highest percentage of subject reported respiratory system disorder was of T+C and T+TKi regimen. In T+TKi+C, infection and infestation were found at a high rate. Few patients in all treatment regimens experienced a decrease in appetite, which was particularly common in the T+TKi regimen. Anaemia, leucopenia, neutropenia, and thrombocytopenia were found in all groups. T+TKi+C regimens had the highest percentage of subjects reporting blood associated disorders followed by Tb. Out of 32 studies, death is reported with biosimilar and T+C.

Repeated electronic searches did not reveal any previous single meta-analysis that assesses and compares the

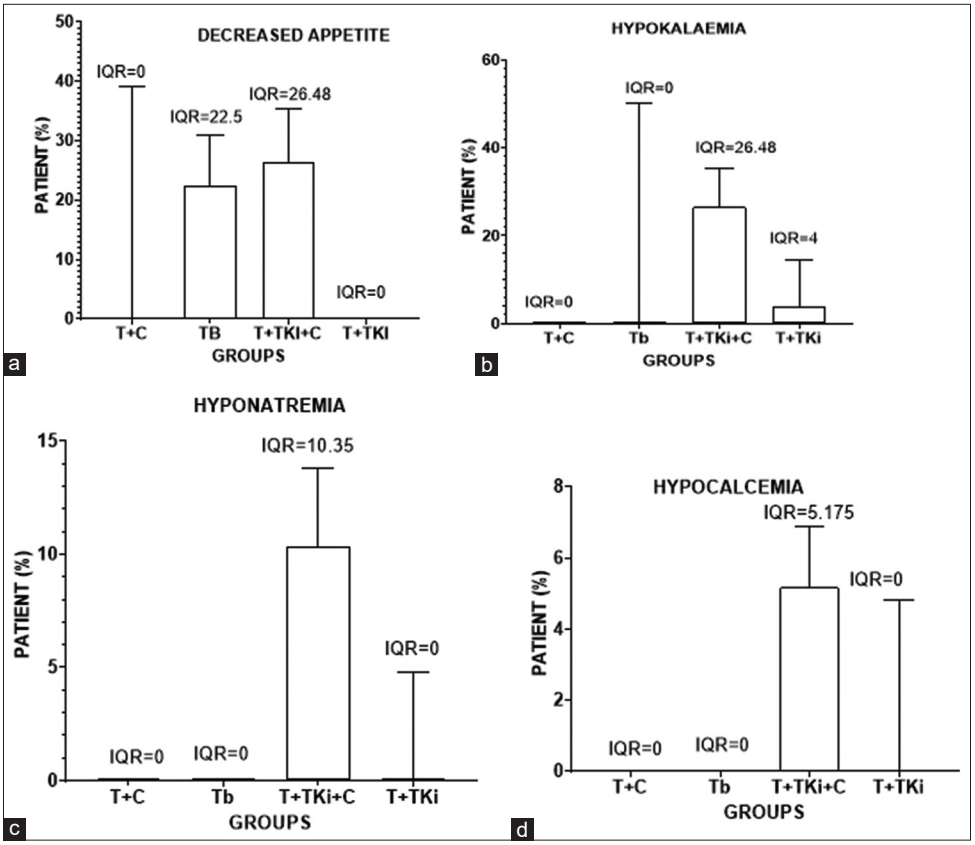

Figure 9: Box and whisker representation of the range of patients in different groups showing (a) decreased appetite, (b) hypokalaemia, (c) hyponatremia and (d) hypocalcaemia.

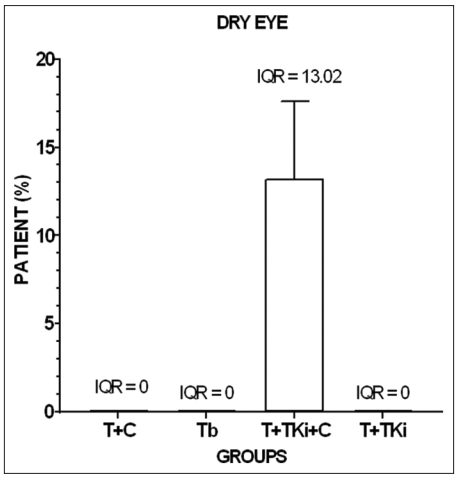

Figure 10: Box and whisker representation of the range of patients in different groups showing dry eye.

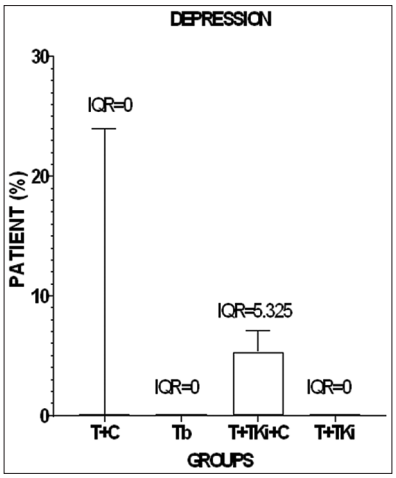

Figure 11: Box and whisker representation of the range of patients in different groups showing depression.

safety of trastuzumab with the various combination used for the treatment of BC. The previous meta-analysis by Dahabreh *et al*. found that the use of trastuzumab benefits in disease control and survival came at the cost of serious cardiovascular AEs, particularly heart failure accompanied by LVEF decline.[48] Furthermore, Abraham J states that the combination of trastuzumab and lapatinib (seems to be a safe treatment option in terms of cardiotoxicity but the lapatinib was associated with two well-documented AEs, diarrhoea and dermatologic toxicity.[40] Similar results are also shown by Xin *et al*. and Xu *et al*. that is, the use of lapatinib and trastuzumab in HER2-positive BC cause skin rash, diarrhoea,

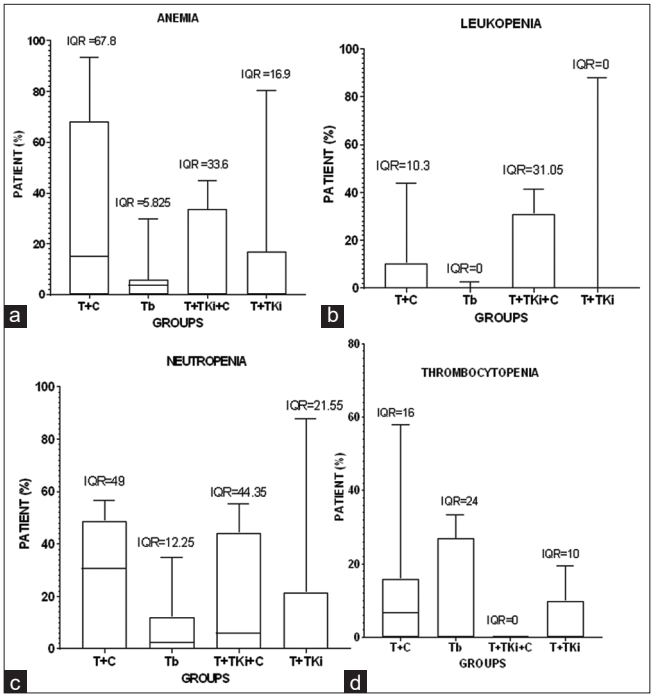

Figure 12: Box and whisker representation of the range of patients in different groups showing (a) anaemia, (b) leucopenia, (c) neutropenia and (d) thrombocytopenia.

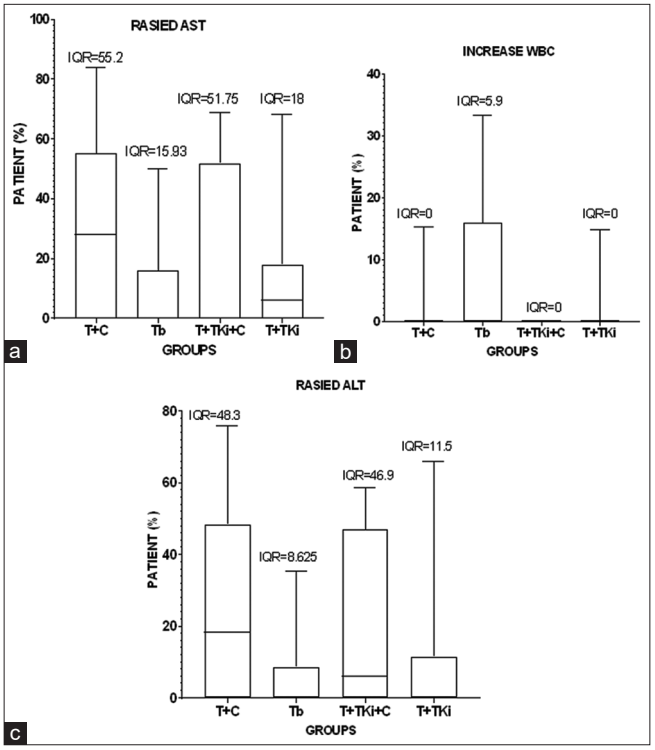

Figure 13: Box and whisker representation of the range of patients in different groups showing (a) increase AST, (b) increase WBC and (c) increase ALT.

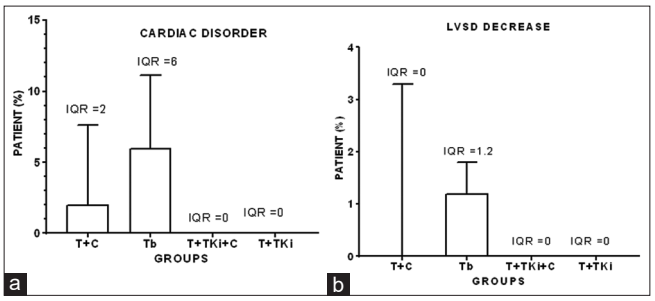

Figure 14: Box and whisker representation of the range of patients in different groups showing (a) cardiac disorder and (b) LSVD decrease.

neutropenia, and hepatic and other AEs.[49,50] Gianni L, Dafni U, *et al*. found that cardiac toxicity was comparable between anti-HER2 combination therapy and anti-HER2 monotherapy.[51]

As we have seen that the previous studies only reported about cardiovascular AEs related to trastuzumab but our study concluded all the systemic AEs along with cardiovascular, more often cardiotoxicity when TKi is given combined with chemotherapy, other systemic toxicities also occur. Furthermore, when chemotherapy is given in this combination, it causes higher systemic side effects. As a result, this study implies that Tb is preferable to alternative medication combinations but the patients must be monitored for cardiovascular toxicity.

Limitations of our study

There are certain limitations to our meta-analysis that should be acknowledged. First limitation is that the number of studies and patients included in some of the outcomes is minimal, reducing the meta-analysis ability to reveal statistically significant results. Our study's second limitation is that the data were gathered from published research rather than from individual patient data (IPD). When compared to IPD studies, meta-analyses based on published data tend to exaggerate treatment effects. However, if all authors do not agree to disclose their whole databases to the analysing group, analyses employing IPD may include fewer research. In general, an IPD-based meta-analysis will provide a more reliable estimate of the correlation.

CONCLUSION

This study concluded that biosimilar of trastuzumab (SB-3 and CT-6P) is safest for the treatment of HER-2-positive BC. Cardiovascular disorder is often reported with biosimilar group, but this group has less AEs reported as compared with chemotherapy, tyrosine kinase inhibitors groups related to other systems such as digestive, nervous, and respiratory.

The choice of combination is depending on the type of BC and the condition of patients. The patients must monitor for cardiotoxicity when the biosimilar of trastuzumab is used.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Kumar D, Basu S, Goyal RK, Sahoo PK, Mathur R. Comparison of adverse effects of trastuzumab with other drug combinations for the treatment of breast cancer: A review. Indian J Physiol Pharmacol 2022;66:1-15.