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Evaluation of the Adverse Effects of Monoclonal Antibodies in Breast Cancer Treatment in a Tertiary Care Hospital in Bengaluru, India, in 2020

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ABSTRACT

Background & Objective: Breast cancer (BC) is the leading cause of cancer mortality among women in different countries around the world, including India. Monoclonal antibodies (MoAbs) have emerged as a promising targeted treatment for BC, improving the survival rate of these patients with minimum adverse effects. This study aimed to investigate the severity of the adverse effects of MoAbs in an Indian population.

Materials & Methods: This longitudinal descriptive study was conducted on 120 BC patients over six months in a tertiary care hospital in Bangalore, India, in 2020. A data collection form was used to gather relevant data. The collected data were analyzed by SPSS Version 21, using Chi-square and Fisher's exact tests. A P-value less than 0.05 was considered statistically significant.

Results: Among 97 patients evaluated in this study (including 29 patients in the non-exposed group), the adverse effects of BC were observed in all age groups. Most adverse effects were attributed to trastuzumab (37.50%; CI: 31.6-44) and bevacizumab (26.78%; CI: 20.9-31.8). The MoAbs were well tolerated by the patients, causing minimum adverse effects that were manageable by supportive therapy. Anemia was the most prevalent adverse effect. Evaluation of the null hypothesis indicated that the adverse effects of MoAbs depended on their amount and composition. The results of analysis using the Naranjo scale revealed that most of the adverse effects were probable (67%) and possible (32%), respectively. Also, according to the WHO scale, most of the adverse effects were under the categories of probable (61.20%) and possible (38.14%), respectively.

Conclusion: Based on the present results, the adverse effects of MoAbs were manageable by supportive care. Anemia was found to be the most prevalent adverse effect. Meanwhile, no potential adverse cardiovascular event was observed in patients on trastuzumab, except one case of dilated cardiomyopathy.

Keywords: Naranjo scale, Monoclonal antibodies, Breast cancer

Introduction

According to the Surveillance, Epidemiology, and End Results (SEER) data, breast cancer (BC) is one of the leading causes of cancer-related mortality in women worldwide. In 2012, BC was responsible for the highest cancer mortality rates in 161 countries (1). By surpassing cervical cancer, BC has become one of the leading causes of mortality among Indian women, with 144,937 new cases reported in 2012. Moreover, it is ranked the most prevalent malignancy among Indian women, with an incidence rate as high as 25.8 per 100,000 women and a mortality rate of 12.7 per 100,000 women (2).

The available treatments for BC include surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Breast conservation surgery is regarded as the best approach for localized BC. Moreover, neoadjuvant therapy is used before surgery to shrink tumors (2). Monoclonal antibodies (MoAbs), which are generated from a single B-lymphocyte clone, are monovalent antibodies, binding to similar epitopes. Kohler and Milstein first discovered MoAbs in 1975 using the hybridoma technology (1) (3), which revolutionized anti-cancer therapeutics in the 19th century.

Chemotherapeutic MoAbs have emerged as standard therapeutic agents against hematological and solid cancers, acting as "targeting missiles" toward cancer cells (2). Moreover, chimeric MoAbs (CMoAbs) are composed of antibodies from two different species. They are less immunogenic than other MoAbs and exhibit more efficient interactions with human effector cells (4). On the other hand, humanized CMoAbs, which are collected

from human sources (90%), are less immunogenic than CMoAbs (4). The adverse effects of naked MoAbs are mild and involve allergic reactions (16). These adverse effects include fever, chills, weakness, headache, nausea and vomiting, diarrhea, low blood pressure, rashes, and in some cases, leucopoenia, thrombocytopenia, and anemia. Studies suggest that conjugated MoAbs cause more adverse events due to immunosuppression; they are also associated with an increased risk of infection and cancer development (5).

The most common adverse effects of atezolizumab, used alongside nanoparticle albumin-bound paclitaxel (Nab-paclitaxel), are peripheral neuropathy, fatigue, nausea, anemia, cough, hypokalemia, pneumonia, and increased aspartate transaminase (AST) levels. The severe adverse effects of this regimen include pneumonia, urinary tract infection (UTI), dyspnea, and pyrexia (6). On the other hand, the common side effects of bevacizumab include hypertension (HTN), asymptomatic proteinuria, thromboembolic events, and gastrointestinal perforation. Additionally, bevacizumab used in combination with sunitinib can cause microangiopathic hemolytic anemia; accordingly, this regimen is not recommended (7). Generally, the most common adverse events of MoAbs include arthralgia, nasopharyngitis, back pain, headache, extremity pain, upper respiratory infection, sore throat, rash, and asymptomatic hypocalcemia (21).

According to previous research, renal failure, dyspnea, pneumonia, and cellulitis are the most common side effects of pembrolizumab (8). Also, cardiac dysfunction, heart failure, and decreased left ventricular ejection fraction (LVEF) are the most probable side effects of targeted HER2 therapy (9). Moreover, the most common side effects of herceptin include fever, nausea and vomiting, diarrhea, infection, cough, headache, fatigue, shortness of breath, skin rash, neutropenia, anemia, and myalgia. Cardiac side effects are also recognized as the most common side effects of trastuzumab (10). In the present study, we aimed to investigate the incidence and severity of the side effects of MoAbs in BC patients and to assess the causality of these adverse events using the Naranjo scale and the World Health Organization (WHO) scale.

Materials and Methods

This longitudinal descriptive study was conducted on 120 BC patients, who were under treatment with MoAbs for six months in a tertiary care hospital of Bangalore, India, in 2020. The study samples were selected using the simple random sampling method, according to the inclusion criteria. To ensure the significance of the results, relevant criteria were considered after calculating the minimum sample size based on the Cohen's formula. All the patients provided informed consent forms to participate in this study.

The patients were diagnosed with locally advanced metastatic BC. They were selected based on the inclusion and exclusion criteria and were followed-up throughout the study. They had received at least one cycle of MoAbs or chemotherapy (exposure and non-exposure groups, respectively) and were followed-up for six months to monitor the incidence of side effects. Only patients with BC were included in this study. On the other hand, patients who were not willing to participate in the study were excluded. The side effects of MoAbs were monitored during the study, and a causality assessment was performed using the Naranjo and WHO scales.

Ethical principles were observed in this research. The names of physicians and patients, as well as the patients' demographic characteristics, remained confidential. To collect data, a standard organization form, containing the patient's demographic information, social habits, medical history, medication history, current use of medications with side effects, drug interactions, and vital signs, was used.

Descriptive statistics were calculated to describe the collected data. For this purpose, the frequency and percentage of qualitative variables, as well as confidence intervals (95% CI), mean, and standard deviation (SD), were measured. Chi-square test, student's samples t-test, and Fisher's exact test were used to analyze the collected data in SPSS Version 21. A P-value less than 0.05 was considered significant.

Ethical Considerations

All information collected from the patients remained confidential in this study. This study was approved by the Narayana Health Academic Ethics Committee (NHAEC) (Code: NHH/AEC/-CL2019-416). It was also registered by the Ethics Committee (EC) (registration number, NO.ECR/772/Inst/KA/2016/RR-19, valid until February 27, 2022), issued under Rule 122 DAC in the Drugs and Cosmetics Rule, 1945.

Results

During the study, a total of 120 women were admitted to our center with a diagnosis of cancer, 97 of whom were diagnosed with BC. The mean age of the patients was 51±7 years, and their average age was 49 years (Table 1). Overall, 40% of the participants were in the age range of 45-55 years (P<0.03). More than 50% of the patients had stage II BC (both clinically and pathologically) at the time of referral (P<0.05). Approximately 60% of cancers had hormone receptors (P<0.04) (Table 2). Only 4% of the patients were HER2-negative, while 42% were HER2-positive, and 54% were unknown. The majority of the patients showed no metastasis (54%). The most common sites of metastasis were the dorsal spine (23%), lungs (13%), and liver (7%), respectively (P<0.05). Based on the findings, trastuzumab and bevacizumab had more side effects than other MoAbs (P<0.02) (Table 3).

Anemia was the most common side effect of all evaluated drugs (37%±12), except pembrolizumab which did not cause anemia. Nausea and vomiting were attributed to all evaluated drugs (21%±7), except

pertuzumab and pembrolizumab. Overall, electrolyte imbalance was detected in 17%±7 of cases, although it was not observed in patients receiving denosumab, atezolizumab, and pertuzumab. Based on the findings, headache and body pain were reported in 11% of the patients. Similarly, fatigue and weakness were reported in 11% of the patients; however, these side effects were not observed in patients receiving trastuzumab. No significant difference was observed in the aggravation of side effects of different regimens and protocols for BC (P>0.06). On the other hand, the prevalence of complications was lower in patients who did not receive trastuzumab (non-exposure group) compared to the exposure group (P<0.003).

Table 1. The age distribution of breast cancer (BC) patients (n=97)

Sl. No.	Age group	Number of patients	Percentage
1	30-40 Years	17	17.53%
2	41-50 Years	25	25.77%
3	51-60 Years	31	31.95%
4	61-70 Years	20	20.61%
5	71-80 Years	4	4.12%

Table 2. The status of hormone receptors in breast cancer (BC) patients (n=97)

Sl. No.	Hormone receptors	Number of cases	Percentage
1	ER positive	30	30.92%
2	ER negative	13	13.40%
3	PR positive	27	27.83%
4	PR negative	16	16.49%
5	Unknown	11	11.34%

ER: Estrogen; PR: Progesterone.

Table 3. The monoclonal antibodies (MoAbs) used in this study and the frequency of side effects

Sl. No.	MoAbs	Number of cases	%	Side effects	%
1	Atezolizumab	1	0.75%	3	5.35%
2	Bevacizumab	18	16.66%	15	26.78%
3	Denosumab	5	4.54%	7	12.50%
4	Pembrolizumab	1	0.75%	6	10.71%
5	Pertuzumab	4	3.78%	4	7.14%
6	Trastuzumab	68	73.48%	21	37.50%

The side effects of MoAbs were monitored in patients throughout the study, and a causality assessment was performed using the Naranjo and WHO scales. The assessment of side effects based on the Naranjo scale revealed that most complications were probable (67%) and possible (32%), respectively. According to the WHO scale, the majority of side effects were also under the categories of probable (61.20%) and possible (38.14%), respectively.

Overall, 19 regimens and protocols were used in the current study. The trastuzumab+paclitaxel regimen was the most frequently used regimen (27.19%), followed by trastuzumab maintenance therapy (18.42%). In all 19 regimens, the most common side effects were anemia, nausea and vomiting, elevated serum globulin levels, and hypocalcemia. On the other hand, the least common side effects were HTN, hypotension, acute kidney injury (AKI), electrolyte imbalance, and body aches. Only one severe adverse event, that is, dilated cardiomyopathy, was detected in one of the patients, due to which trastuzumab was discontinued. According to this finding, the regimens were well tolerated by the patients, with few manageable side effects (Table 4). Moreover, the analysis of the null hypothesis of this study indicated that the side effects depended on the amount and composition of drugs. This finding refutes our assumption and suggests that the frequency of side effects is lower when the amount of drugs is low or when the constituents are few.

Table 4. Treatment protocols for breast cancer (BC) patients (n=97)

Sl. No.	Therapeutic approach	Number of cases	Percentage
1	Atezolizumab+carboplatin	1	0.87%
2	Carboplatin+paclitaxel	2	1.75%
3	Carboplatin+docetaxel+trastuzumab	9	7.89%
4	Carboplatin+gemcitabine+trastuzumab	1	0.87%
5	Carboplatin+docetaxel+pertuzumab+trastuzumab	2	1.75%
6	Denosumab+fulvestrant	1	0.87%
7	Denosumab+paclitaxel	2	1.75%
8	Denosumab+trastuzumab	3	2.63%
9	Docetaxel+trastuzumab	13	11.40%
10	Doxorubicin+cyclophosphamide	10	8.77%
11	Eribulin+trastuzumab	2	1.75%
12	Gemcitabine+zoledronic acid+trastuzumab	5	4.38%
13	Paclitaxel+pertuzumab	1	0.87%
14	Paclitaxel+zoledronic acid+trastuzumab	2	1.75%
15	Trastuzumab	21	18.42%
16	Trastuzumab+paclitaxel	31	27.19%
17	Trastuzumab+pertuzumab	1	0.87%
18	Trastuzumab+zoledronic acid	4	3.50%
19	Trastuzumab+paclitaxel+pertuzumab+zoledronic acid	3	2.63%

Discussion

In the present study, we evaluated the causality of the side effects of MoAbs in patients with BC and gynecologic cancers. The most common side effects were identified, and their severity was examined using the WHO and Naranjo scales. We also discussed the treatment regimens for these side effects **(8, 11)**. According to the present findings regarding the clinical stage of BC, out of 97 patients, 10.30% had stage I BC, 52.57% had stage II BC, 28.86% had stage III BC, and 8.24% had stage IV BC, which indicates the predominance of stage II BC, followed by stage III BC. In this regard, a study by Iago Dillion Lima Cavalcanti et al. in 2017 showed the predominance of stage III BC, while no stage IV cases were detected **(9, 10)**.

Moreover, in the present study, the hormone receptor status was evaluated in all 97 BC patients. Based on the results, 30.92% of the patients were ER-positive, 13.40% were ER-negative, 27.83% were PR-positive, 16.49% were PR-negative, and the remaining 11 cases were unknown. In a study by Huszno et al. in 2013, ER expression was identified in 66 (55%) patients, while PR expression was found in 55 (45%) patients **(10, 12, 13)**.

Regarding the clinical tumor (T) stage of BC in our study, 3.098% of the patients were in T_1 stage, 21.64% were in T_2 stage, 2.06% were in T_3 stage, 4.12% were in T_4 stage, 3.09% were in T_4d stage, and 69.07% were unknown. In a study by Hussain et al. in 2018, clinical T staging was compared between the docetaxel /carboplatin/trastuzumab/pertuzumab (TCHP) and docetaxel/carboplatin/trastuzumab (TCP) regimens. The results showed that T_2 stage was the most common stage in both regimen groups. In this study, there were only two patients with T_2 stage receiving the TCHP regimen, while there were nine T_2 stage patients receiving the TCP regimen; the rest of the patients were above T_2 stage **(10, 14, 15)**.

In the present study, the metastasis status of 97 BC patients was investigated. Based on the results, bone metastasis occurred in 8.24% of the patients, brain and bone metastasis in 3.09% of the patients, liver metastasis in 6.18% of the patients, liver, lung, and bone metastasis in 10.30% of the patients (n=10), liver and lymph node metastasis in 1.03% of the patients, lung metastasis in 6.18% of the patients, lung and bone metastasis in 3.09% of the patients, and lymph node and bone metastasis in 4.12% of the patients; also, 57.73% of the patients were non-metastatic. The

findings indicated that the incidence of liver, lung, and bone metastasis was the highest, followed by bone metastasis, liver and lung metastasis, lymph node and bone metastasis, lung and bone metastasis, brain and bone metastasis, and finally, liver and lymph node metastasis. In a study by Esin et al. in 2018, the frequency of liver and lymph node metastasis was the highest (23.1%), followed by lung and bone metastasis (19.2%), lung and lymph node metastasis and liver and bone metastasis (15.4%), brain, liver, and lung metastasis, lung metastasis, and liver and lung metastasis (7.7%), and finally, liver metastasis (3.8%) **(14, 16)**.

In the current study, we evaluated the side effects of trastuzumab in BC patients. According to the results, trastuzumab was well tolerated by the majority of the patients. Overall, 21 side effects were detected, among which anemia was the most common (49.26%), followed by nausea and vomiting (17.64%), hypocalcemia (7.35%), and elevated serum globulin levels (4.41%). However, some of the side effects were less frequent and required further attention. Dilated cardiomyopathy was detected in one of the patients, after which trastuzumab was discontinued due to cardiomyopathy. In this regard, Kistler (2014) reported that trastuzumab carries a black box warning for cardiomyopathy/heart failure; these patients may be either symptomatic or asymptomatic. Also, the less common side effects were abnormal liver function tests, odynophagia, AKI, alopecia, bronchiectasis, electrolyte imbalance, HTN, hypermagnesemia, hypocalcemia, hypotension, insomnia, lymphedema, mucositis, myalgia, polyuria, pyelonephritis, and ulcer **(15, 17)**.

Conclusion

In this study, most side effects of MoAbs were under the categories of probable (61.20%) and possible (38.14%), respectively. However, none of the side effects were severe; in other words, MoAbs were well tolerated by the patients. The side effects were manageable via supportive care. Based on the results, anemia was the most common adverse effect. No potential adverse cardiovascular events were detected in patients on trastuzumab, expect one case of dilated cardiomyopathy. Further research is required to obtain more accurate results.

Author's Contributions

All authors equally contributed to the preparation of this article.

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Conflict of Interest

The authors declare no conflicts of interest.

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