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Assesment of Safety Profile of Immunotherapeutic Agents other than Immune Checkpoint Inhibitors in Cancer Patients

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Abstract

Introduction: Immunotherapy is a form of oncologic treatment directed towards enhancing the host immune system against cancer. Immunotherapeutic agents were significantly associated with a higher risk of developing adverse effects in cancer patients. Bevacizumab was significantly associated with higher risk of developing venous thromboembolism, GI perforation such as bleeding and leukopenia in cancer patients. Trastuzumab has led to a significant improvement in the treatment of both advanced and early breast cancer by over expressing HER-2 receptors. It was associated with an important adverse effect, cardiotoxicity. Cetuximab and Panitumumab are monoclonal antibodies targeting the endothelial growth factor receptors (EGFR) currently used for systemic treatment of metastatic colorectal cancer in combination or alone have been reported to be able to induce skin toxicities. Nausea, diarrhea and rash were the most common adverse effects in Pertuzumab alone and Pertuzumab – based therapies. Pertuzumab also increases the risk of clinical heart failure, but not asymptomatic/minimally symptomatic left ventricular systolic dysfunction, in HER2-positive cancer patients. ***Materials and Methods***: An ambispective observational single center study was conducted by collecting details of patients prescribed with Trastuzumab, Bevacizumab Pertuzumab, cetuximab and panitumumab. Retrospective study period of 5 years (2017 November to 2022 November) and Prospective study period of 6 months were conducted (December 2022 to May 2023). Patients of all age groups prescribed with immunotherapeutic agents other than immune checkpoint inhibitors was included and patients who were discharged against medical advice and incomplete data was excluded. ***Results***: Majority of patients in our study were in age groups of 56-65 years with 38.5%. Among 65 patients, 4 of them reported with trastuzumab induced cardiotoxicity and 3 of the patients taking trastuzumab along with pertuzumab also reported with cardiotoxicity. Among 30 patients who were taking bevacizumab, one patient was reported with pneumonitis. We conducted a correlation analysis using chi-square test between study considered drugs and the reported adverse reactions. All of the patients prescribed with Trastuzumab + Pertuzumab were having ADR. Also, majority of the patients prescribed with Bevacizumab were not having ADR. Since the p-value of chi-square test was found to be <0.001 so there exist a significant relation between drugs prescribed and ADR. ***Conclusion***: We assessed the safety profile of immunotherapeutic agents other than immune check point inhibitors in cancer patients. We also correlated the study considered drugs and adverse drug reaction occurrence, there existed a significant correlation.

Keywords: Trastuzumab, Bevacizumab, Pertuzumab, Cetuximab, Panitumumab, Cardiotoxicityand Pneumonitis.

INTRODUCTION

According to WHO the adverse drug reaction is defined as the response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function. Malignant cells have the capacity to rapidly grow exponentially and spread in part by suppressing, evading and exploiting the host immune system. Immunotherapy is a form of oncologic treatment directed towards enhancing the host immune system against cancer. In recent years a number of new molecules commonly known as biological therapies have been approved for the treatment of various cancers. These innovative compounds have improved treatment efficacy and have probably contributed to increase in survival length. However, these agents are not deprived of toxicity, which can

impair quality of life and may occasionally be life threatening. Immunotherapeutic agents were significantly associated with a higher risk of developing adverse effects in cancer patients [1].

Bevacizumab was significantly associated with higher risk of developing venous thromboembolism in cancer patients. Other clinically relevant adverse effects such as GI perforation such as bleeding and leukopenia. Trastuzumab has led to a significant improvement in the treatment of both advanced and early breast cancer by over expressing HER-2 receptors. It was associated with an important adverse effect cardiotoxicity [2].

Pertuzumab is a novel humanized monoclonal antibody that blocks human epidermal growth factor receptor 2 (HER-2) dimerization. The Food and Drug Administration has approved Pertuzumab in combination with Trastuzumab and docetaxel for the treatment of patients with HER-2 positive metastatic breast cancer. Nausea, diarrhea and rash were the most common adverse effects in Pertuzumab alone and Pertuzumab – based therapies [3].

Cetuximab and Panitumumab are monoclonal antibodies targeting the EGFR currently used for systemic treatment of metastatic colorectal cancer in combination or alone have been reported to be able to induce skin toxicities. In this study we assess the safety profile of immunotherapeutic agents other than immune checkpoint inhibitors [4].

MATERIALS AND METHODS

An ambispective observational single center study was conducted by collecting details of patients prescribed with Trastuzumab, Bevacizumab Pertuzumab, cetuximab and panitumumab. Retrospective study period of 5 years (2017 November to 2022 November) and Prospective study period of 6 months were conducted (December 2022 to May 2023). The study was started after receiving approval from the institutional ethics committee. Eligible patients gave written informed consent before to enrolment.

Inclusion Criteria: Patients of all age groups prescribed with immunotherapeutic agents other than immune checkpoint inhibitors.

Exclusion Criteria

1. Patients who were discharged against medical advice
2. Patient with incomplete data

Statistical Analysis

The data collected was compiled using Microsoft Excel and presented using bar graphs to visualise the information. Calculations for the mean and standard deviation were conducted using statistical calculators. To perform statistical analysis, the data was imported into SPSS, a statistical software program.

RESULTS

Majority of patients in our study were in age groups of 56-65 years with 38.5%. The mean age of patients was 57.107 ± 10.409 years.18.5% of cases were in an age group of 36-45 years,20% of cases were in 46-55 years, 38.5% of cases were in 56-65 years, 21.5% of cases were in 66-75 years and 1.5% of cases were in above 75 years.

Out of 65 cancer patients, 43 of them were female and 22 of them were male. The population had a significantly higher proportion of female (65%). The frequent type of cancer in females was breast cancer in 27 patients (62.8%). Most of the patients were having family history of breast cancer. The second most prevalent was ovarian cancer in 6 patients (14%) and two patients were having rectum cancer, colon cancer and lung cancer (4.7%). Endometrial cancer was found to be in 1 patient (2.3%). The oropharynx, tongue, vocal cord cancer accounted for 3 patients. The most frequent type of cancer in male was in oropharynx, tongue and vocal cord which was in 7 patients (31.8%) and the second prevalent one was found to be hepatocellular and colon cancer which was in 5 patients (22.7%). Rectum cancer and renal cell carcinoma in 2 patients each (9.1%) and lung cancer in 1 patient (4.5%).

Out of 65 cancer patients included, 24 of them doesn't have comorbidities and 41 of them had comorbidities.23 patients were presented with 1 comorbidity ,9 patients with 2 comorbidities, 8 patients with 3 comorbidities and 1 patient with more than 3 comorbidities. Among these mostly reported comorbidities were Hypertension, DM and Thyroid disorders. [Table 2]

Of all the 65 patients taking immunotherapeutic agents other than immune checkpoint inhibitors 8 ADR was reported. The most common reported ADR was 7 cardiotoxicity (87.5%) and a patient with pneumonitis (12.5%). [Figure 1]

Among 65 patients, 4 of them reported with trastuzumab induced cardiotoxicity which was 21.05% and 3 of the patients taking trastuzumab along with pertuzumab also reported with cardiotoxicity (100%). The patients who were taking trastuzumab had comorbidities like HTN (Hypertension), DM (Diabetes Mellitus), DLP (dyslipidaemia) and in patients who were taking trastuzumab along with pertuzumab had comorbidities like HTN and Thyroid disorders. Age group were found to be above 50 years. Following initiation, 4 reported cardiotoxicity which was developed within 3 years. In the cardiotoxicity cases, 2 of them were on conventional therapy with Taxanes, Cyclophosphamide and capecitabine. Among 30 patients who were taking bevacizumab, one patient was reported with pneumonitis. [Table 1]

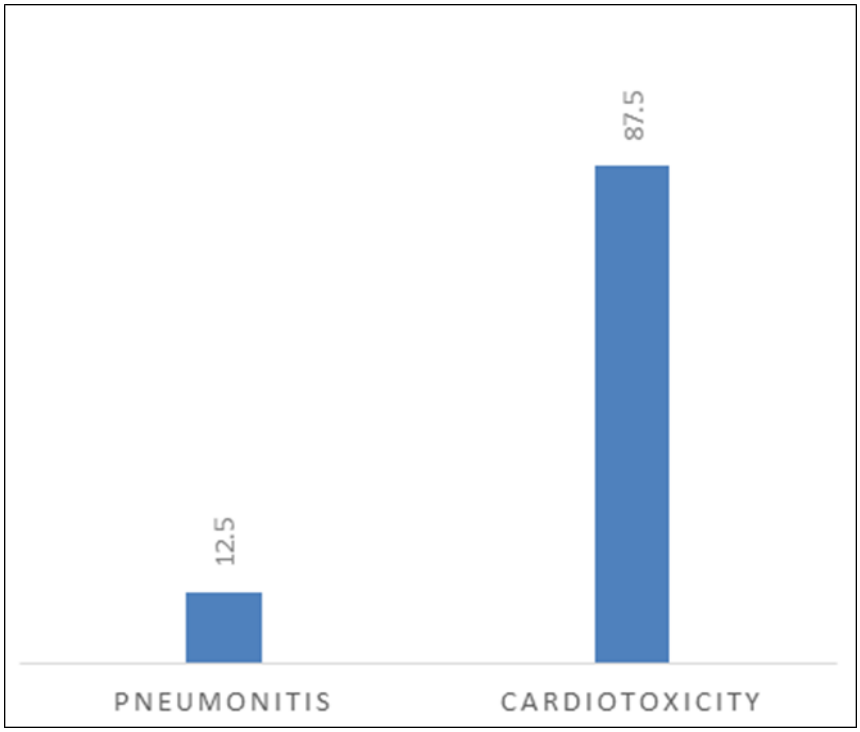

Fig. 1: Distribution of Cancer Patients based on type of ADR Reported

Table 1: Distribution of ADR among patients based on selected immunotherapeuticagents

Drug	ADR	Frequency	Percentage (%)
Trastuzumab	Cardiotoxicity	4	50%
Bevacizumab	Pneumonitis	1	12.50%
Trastuzumab + Pertuzumab	Cardiotoxicity	3	37.50%

Of the 6 cardiotoxicity cases patients were advised for periodic monitoring of cardiovascular events and one patient who have LVEF 45% management was done by initiation of Betablockers and HCN- channel blocker (Hyperpolarization- activated cyclic nucleotide-gated channel). Bevacizumab induced pneumonitis was managed by giving antibiotics for 5-8 days and inj. Hydrocortisone, not much response was found so Inj. Methylprednisolone was administered, the condition of the patient got improved then inj. Methyl prednisolone was slowly tapered and switched to Tab. Methyl prednisolone. We conducted a correlation analysis using chi-square test between study considered drugs and the reported adverse reactions. All of the patients prescribed with Trastuzumab + Pertuzumab were having ADR. Also, majority of the patients prescribed with Bevacizumab (96.6%) were not having ADR. Since the p-value of chi-square test was found to be <0.001 so there exist a significant relation between drugs prescribed and ADR. [Table2]

Table 2: Correlation between study considered drugs and ADR reported

Study considered drug	ADR		Total	$\times^2$	df	p-value
	No	Yes				
Trastuzumab	15	4	19			
Bevacizumab	29	1	30			
Cetuximab	8	0	8			
Panitumumab	3	0	3			
Trastuzumab + Pertuzumab	0	3	3	26.78	7	<0.001
Trastuzumab + Bevacizumab	1	0	1			
Bevacizumab + Panitumumab	1	0	1			
TOTAL	57	8	65			

Out of 65 patients 2 patients reported with cardiotoxicity in stage 2, five patients in stage 3 and one patient reported with pneumonitis in stage 4. [Table 3]

Table 3: Distribution of ADR'S based on Stage of Cancer

Stage	Number of ADR	Type of ADR
Stage 2	2	Cardiotoxicity
Stage 3	5	Cardiotoxicity
Stage 4	1	Pneumonitis

Among 65 cancer patients, 27 patients were having breast cancer, among that 7 patients reported ADR and 20 of them doesn't reported with ADR. Of the 7 ovarian cancer patients in our study 1 patient reported with ADR.

DISCUSSION

Majority of patients in our study were in age groups of 56-65 years. A similar study conducted by Swathi Gopi Shetty et al on age and race distribution in patients in phase III Oncology clinical trials. In this study patients with age greater than 75 years showed an increasing frequency of cancer, which is found to be similar to our study [5]. Gamal Mostafa et al conducted a cohort study on influence of demographics on colorectal cancer. In this study the female population have a larger proximal lesion and was poorly differentiated. The probability for a proximal tumor in female greater than 70years was 61.9% and in white male greater than 50years was 35.1% [6].

Among breast cancer patients undergoing adjuvant chemotherapy, those treated with trastuzumab-based/anthracycline- based regimens had increased cardiotoxicity risk. An initiation of ACEIs/BBs in those receive adjuvant trastuzumab/anthracyclines may prevent cardiotoxicity and improve survival [7]. Prior exposure to anthracyclines and prior left ventricular dysfunction with trastuzumab treatment may be potential risk factors of cardiac toxicity for patients who are treated with trastuzumab plus pertuzumab. Cardiac status should be closely monitored in future clinical trials using this combination treatment [8].

In a case report describing Bevacizumab-induced pneumonitis,was managed with broad-spectrum antibiotics and IV Methylprednisolone 60mg every 8 hours; subsequently,patients condition improved, and was extubated within two days of corticosteroid therapy initiation and was transitioned to daily oral Prednisone 40 mg [9]. Kiyohiko et al., conducted a post-approval surveillance study on bevacizumab safety in Japanese patients with colorectal cancer. A total number of 2696 patients were included in the safety analysis. ADR of interest with bevacizumab were reported in 738 patients (27%) [10].

CONCLUSION

The use of cancer immunotherapeutic agents to stimulate the immune system to recognize and attack malignancies has provided new possibilities for effective cancer treatment. The last few decades have seen the development of a range of novel and effective immunotherapies, broadening oncologistschoice of weapons to fight cancer. Hence, we assessed the safety profile of immunotherapeutic agents other than immune check point inhibitors in cancer patients. Our study analysed the safety profile of immunotherapeutic agents. We also correlated the study considered drugs and adverse drug reaction occurrence, there existed a significant corelation. Our study concluded that, The ADRs of immunotherapeutic agents were found to be limited; drug-induced cardiotoxicity has been reported with the use of Trastuzumab. Additionally, the combination of Trastuzumab with Pertuzumab and Bevacizumab has been found to induce pneumonitis. Severe cardiotoxicities were managed by using beta blocker, ivabradine and pneumonitis managed with inj. methyl prednisolone. Based on the type of cancer, an assessment was made on the safety profile of immunotherapeutic agents. More number of cardiotoxicities as ADR were reported in breast cancer and pneumonitis as ADR was reported in a patient with Ovarian cancer. The report edcardiotoxicity was observed in stage II and stage III and pneumonitis was observed in stage IV.

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