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Cardiotoxicity and Other Adverse Effects of Immune Checkpoint Inhibitors

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Abstract

Background: Immune checkpoint inhibitors (ICI) usage has increased in recent years, along with it the associated adverse effects.
Objective: To conduct an observational study on immune checkpoint usage and adverse drug reactions associated with its use in a tertiary care center from coastal south India.
Methodology: 228 patients were enrolled in this ambispective study, patient's data was collected from the year 2020-2024. Patients were selected based on inclusion criteria.
Results: While adverse effects such as pruritus, tachycardia, and thyroiditis occurred infrequently, their clinical significance necessitates careful monitoring. A statistically significant association (p = 0.022) between treatment response and adverse events indicated a potential relationship between therapeutic effectiveness and toxicity. The instance of myocarditis was found to be 0.4%.
Conclusion: These findings emphasize the significance of accurate monitoring, management, which includes various fields, and individualized therapies to maximize the outcomes for patients and reduce potential risks associated with Immune Checkpoint inhibitors (ICI).

Keywords: Immune checkpoint inhibitors, cardiotoxicity, myocarditis, immune-related adverse events

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INTRODUCTION

Cancer continues to be a primary contributor to mortality rates in our country. Conventional treatments, including surgery, chemotherapy, and radiation therapy, have been widely employed; however, they come with notable disadvantages. Despite significant progress in recent years, both chemotherapy and radiation frequently result in cytotoxic effects that harm healthy cells, while only targeting a small percentage of cancer cells[1].

Over the past two to three decades, oncology has experienced significant advancements with the introduction of innovative therapies such as checkpoint inhibitor immunotherapy, proton therapy, and robotic surgery. Checkpoint inhibitors have shown consistent overall survival benefits across various clinical settings, as evidenced by randomized trials[2]. Immunotherapy has notably broadened the range of available cancer treatments[3]. Nonetheless, tumours can evade immune detection through various mechanisms, including the upregulation of inhibitory signals, the secretion of immunosuppressive cytokines, or the downregulation of antigen expression[4]. It is important to note that immune checkpoint inhibitors (ICIs) can be safely administered to patients with multiple comorbidities, including those with HIV, influenza, or SARS-CoV-2 infections[5].

Drugs in this category, including CTLA-4 inhibitors like ipilimumab and PD-1/PD-L1 inhibitors such as nivolumab and pembrolizumab, function by activating suppressed T-cell activity. This enhancement allows the immune system to more effectively target and eliminate tumour cells, leading to sustained responses in various cancer types[6]. The long-term evidence derived from early ICI trials is encouraging, as a subset of patients with metastatic cancer has demonstrated enhanced survival rates even at the five-year mark[7].

Organizations like the Canadian Agency for Drugs and Technologies in Health offer dosing recommendations based on pharmacokinetic modelling to enhance the utilization of ICIs. Researchers in Europe have proposed strategies such as vial sharing and weight-based dosing to optimize costs and decrease drug waste[8]. In India, these medications were launched only a few years prior. Nonetheless, the elevated expenses have constrained broad implementation, and most clinical practices are informed by Western research. The absence of published real-world data regarding their safety and efficacy within the Indian population is essential to substantiate their costs and the potential for immune-related adverse effects (IrAEs)[9].

Immune checkpoint inhibitors can lead to a range of cardiotoxic effects as a result of extensive immune activation among the immune-related adverse events. While infrequent, these cardiac complications hold clinical significance. ICI-induced cardiotoxicity includes conditions such as myocarditis, pericarditis, arrhythmias, and heart failure. Myocarditis represents a serious condition, impacting 0.27–1.14% of patients and associated with a mortality rate exceeding 40% if left untreated. The underlying mechanism is believed to involve T-cell-mediated inflammation targeting cardiac tissue, indicative of the autoimmune activation triggered by immune checkpoint inhibitors. Factors that contribute to risk encompass prior cardiovascular conditions, the use of combination immune checkpoint inhibitor therapy, and genetic predispositions[10].

The American Society of Clinical Oncology (ASCO) categorizes ICI-associated myocarditis into four grades, determined by severity, clinical presentation, and diagnostic findings:

G1: Cardiac biomarkers are abnormal, but the patient is asymptomatic and has a normal ECG.

G2: Cardiac biomarkers are abnormal, and the patient has either mild symptoms or new ECG changes that do not include conduction delays.

G3: Cardiac biomarkers are abnormal, and the patient experiences either moderate symptoms or develops new conduction delays on the ECG.

G4: The patient is moderately to severely decompensated, needs intravenous therapy or other medical intervention, or is facing life-threatening conditions.[11,12]

METHODOLOGY

This study was conducted in a tertiary care center in Southern India. This was an ambispective observational study with the aim of tracking patients on treatment with immune checkpoint inhibitors. We gathered data retrospectively from the patients between January 2020 and November 2023 from different sources, such as cardiology reports, clinical performas, and hospital health information system data, whereas patients who were started on immune checkpoint inhibitors were prospectively studied for four months. We selected patients based on the inclusion and exclusion criteria. Patients treated with immune checkpoint inhibitors (ICIs) were included, while those not meeting

electrocardiographic (ECG), imaging, and biomarker criteria were excluded. Based on the findings of an existing literature study on cardiovascular events following the introduction of immune checkpoint inhibitors, (13) the required sample size came out to be 186 patients with 95% confidence and 5 units absolute precision, we were able to include 228 patients into our study based on the available health system data. Patients were assessed for cardiotoxicity and other adverse effects. Statistical significance was assessed using the chi-square test and the independent samples t-test. Statistical analysis was conducted using SPSS version 30.

RESULTS

Baseline Characteristics

The median age of the 228 patients in this retrospective study was 62 years, with a range from 9 to 87 years. Most participants were male (68.4%). 86% of patients exhibited non-metastatic disease, whereas thirteen percent presented with metastases. Histocellular carcinoma constituted 27.1% of all cases; lung cancer represented 19.8%, and head and neck cancers, especially tongue and pharyngeal cancers, were the predominant types of primary cancer. Histologically, genitourinary cancers were the most prevalent, comprising 33.7% of the total, followed by lung cancers at 30.7%, and then melanomas and sarcomas at 9.9%. A heterogeneous cohort of patients was administered immune checkpoint inhibitors (ICIs), as indicated by the variety of oncological conditions represented.

Table 1. Baseline characteristics

	N=228
Age (median-range)	62 y (9–87)
Sex	
Male	156 (68.4%)
Female	72 (31.6%)
Metastasis	
Metastatic	34 (13.6%)
Non-metastatic	216 (86.4%)
Diagnosis	
Renal cell carcinoma (RCC)	10 (10.4%)
Hodgkins Lymphoma	4 (4.2%)
Cholangiocarcinoma (including intrahepatic)	2 (2.1%)
Gall bladder cancer	1 (1.0%)
HCC + BCLC C and BCLC D	26 (27.1%)
Ca Lung	19 (19.8%)
Ca Tongue	7 (7.3%)
Ca prostate	1 (1.0%)
Ca stomach	3 (3.1%)
Ca breast	4 (4.2%)
Ca esophagus	6 (6.2%)
Ca tonsil	1 (1.0%)
Endometrial Ca	3 (3.1%)
Urothelial Ca	3 (3.1%)
Ca Ovary	1 (1.0%)
Ca pharynx	3 (3.1%)
Leptomeningeal	1 (1.0%)
Embryonal germ cell ca	1 (1.0%)
Histology	
Lung Cancers.	31(30.7)
Gastrointestinal (GI) Cancers.	8 (7.9%)
Genitourinary (GU) Cancers.	34 (33.7%)
Head & Neck Cancers.	9 (8.9%)
Breast & Gynecological Cancers.	9 (8.9%)
Melanomas & Sarcomas.	10 (9.9%)

Treatment and Response

Nivolumab (41.6 percent) and pembrolizumab (35.08 percent) were the most frequently utilized immune checkpoint inhibitors. Atezolizumab and durvalumab usage came out to be (19.7%) and (3.5%) respectively. Outcomes from therapy were inconsistent, with over half of the patients (56.1%) encountering disease progression. Partial responses (3.07%) and complete response (8.3%) were infrequent, and 11.8% expired during treatment. While the majority (56.1%) experienced progression, 2.6% of patients experienced relapse or inadequate response following initial improvement. Notably, 17.9% of patients were lost to follow-up, potentially impacting long-term outcomes.

Adverse drug reactions

Adverse drug reactions (ADRs) linked to immune checkpoint inhibitors (ICIs) in this cohort were typically rare but exhibited diverse manifestations, impacting various organ systems. The most frequently reported adverse drug reaction was pruritus, noted in 4.3% of patients, closely followed by tachycardia and fatigue, each occurring in 3.9% of cases. Gastrointestinal disturbances occurred in 2.19% of patients, while metabolic complications, including electrolyte imbalance (1.7%) and diabetes (1.31%), were also observed. Hematologic toxicities, such as leukopenia (1.7%), and mucocutaneous adverse effects, including oral ulcers (1.75%), were infrequent, however clinically significant. Endocrine-related adverse effects, although infrequent, contained thyroiditis (1.3%), consistent with established immune-mediated thyroid dysfunctions linked to immune checkpoint inhibitors (ICIs). Diabetes also occurred at the same frequency (1.31%). Hepatitis, a potentially

serious immune-related adverse event, occurred in 0.88% of the population. Neurological toxicity was negligible, with delirium noted in only one patient (0.43%). The major cardiac adverse effect associated with immune checkpoint inhibitors, myocarditis, occurred in one patient (0.43%). The diverse immune-related toxicities observed emphasize the necessity for close surveillance for patients on immune checkpoint inhibitors.

There was a significant response observed between response to treatment and adverse effects with a p-value of 0.022, which indicates that a patient's response to treatment could be associated with the adverse events they encounter. The instance of myocarditis was found to be 0.4%

Table 2. Immune checkpoint Inhibitors

Table 2	**N=228**
Nivolumab	95 (41.66)
Pembrolizumab	80 (35.08)
Atezolizumab	45 (19.73)
Durvalumab	8 (3.508)

Table 3. Response to treatment

	N= 228
Disease Progression	128(56.14)
Partial response	7(3.07)
Poor response/Relapse	6(2.63)
Death	27(11.8)
Good Response	19(8.33)
Lost to follow up	41(17.98)

Table 4. Adverse Drug reactions

Cardiac	
Tachycardia	9 (3.9)
Myocarditis	1 (0.43)
Non- Cardiac	
Pruritus	10 (4.3)
Fatigue	9 (3.9)
GI disturbance	5 (2.19)
Electrolyte Imbalance	4 (1.75)
Leukopenia	4(1.75)
Mouth Ulcer	4 (1.75)
Diabetes	3 (1.31)
Thyroiditis	3 (1.31)
Hepatitis	2 (0.877)
Delirium	1 (0.43)

DISCUSSION

The advent of immune checkpoint inhibitors (ICIs) has revolutionized cancer therapy by enhancing survival across a broad spectrum of cancers. Their immune-mediated action, however, also subjects patients to a range of irAEs, some of which are severe or life-threatening[6,14]. The most frequent irAE in our study was pruritus (4.3%), consistent with international experience pointing to dermatologic toxicities like psoriasis form eruptions and lichenoid reactions as among the most common[15]. A case report published in 2023 described a patient undergoing cancer treatment who experienced abrupt oxygen desaturation and widespread erythema secondary to a hypersensitivity reaction to atezolizumab. A desensitization protocol was subsequently repeated for each treatment cycle, allowing continuation of therapy without recurrence of significant reactions to subsequent doses.[16]

Cardiac presentations, such as tachycardia (3.9%) and myocarditis (0.43%), as rare as they are, warrant special mention by virtue of their potentially life-threatening nature. The incidence of observed myocarditis at 0.4% aligns with international reports from the FDA FAERS and WHO VigiBase of rates between 0.27% and 1.14%, and consequent mortality in excess of 40% if not treated[10,17]. This underscores the need for early diagnosis and prompt action. A previous study has shown that a hs-CRP threshold of 2 mg/L is a significant predictor of major adverse cardiac vascular events, with those who have it 19 times more likely to experience severe events[18]. This underscores the need for early diagnosis and prompt action. Our experience of myocarditis was in a patient who was a female with metastatic adrenocortical carcinoma on pembrolizumab and developed heart failure and ultimately died of multiorgan dysfunction emphasizing the severity of ICI-related myocarditis[19]

Endocrine irAEs like thyroiditis (1.3%) and diabetes mellitus (1.3%) were noted, in accordance with literature that reports thyroiditis as the most common endocrine side effect of ICI therapy[20,3] . Pembrolizumab, however, has been most associated with an increased frequency of immune-related diabetes[21,22] and were thus seen in our cohort. Gastrointestinal side effects and hematologic toxicities were also uncommon but were clinically relevant. Electrolyte disturbances, such as hyponatremia, were noted and are being increasingly described as among the ICI toxicity syndrome[23].

We also observed mucosal toxicities, such as oral ulceration and upper GI tract involvement, in a few patients. Earlier reports have described a greater-than-expected incidence of oral side effects in ICI recipients[24,25]. In addition, two instances of hepatitis

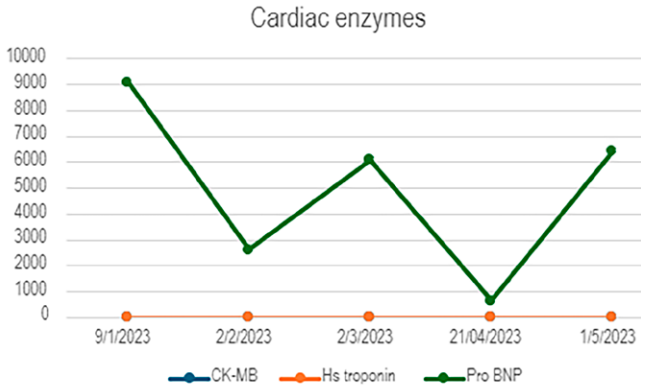

Figure 1: Changes in cardiac function test for myocarditis patient

arose during nivolumab treatment. Although uncommon, nivolumab-induced hepatotoxicity has been reported and is believed to occur via mechanisms such as T-cell–mediated hepatic injury[26,27].

Notably, a statistically significant correlation (p=0.022) between the presence of adverse events and response to treatment was noted. This finding validates earlier hypotheses that irAEs can serve as surrogates for efficient immune activation and thus associate with favorable treatment response[10,17]. Nevertheless, by virtue of the exploratory nature of our analysis, this correlation needs validation in a larger patient population.

LIMITATIONS

Our study is subject to several important limitations that should be considered when interpreting the findings. The relatively small sample size (n = 228) restricts the generalizability of our results, particularly for rare events such as myocarditis. Additionally, the prospective follow-up period was limited to only four months, which may only detect acute toxicities and be insufficient to detect delayed-onset immune-related adverse events (irAEs), especially those involving cardiac or endocrine systems that can manifest later. Cardiac assessments predominantly relied on echocardiograms and biomarkers, while the more sensitive cardiac MRI was not consistently utilized, potentially leading to under-detection of myocarditis. Furthermore, our analysis was exploratory in nature and did not include multivariate adjustments for possible confounders such as baseline cardiac conditions, tumor size, or concurrent therapies. The lack of a control or comparison group restricts the ability to draw causal conclusions. There was also inconsistency in the application of the cardiac work-up algorithm across patients, which could impact the uniformity of cardiotoxicity detection and reporting. These limitations highlight the need for larger, multicenter studies with standardized assessment protocols to provide more definitive insights.

CONCLUSION

This real-life experience from a tertiary center in Southern India gives an insight into the safety profile of immune checkpoint inhibitors in various malignancies. Although the majority of immune-related adverse effects were rare, their clinical significance particularly cardiac and endocrine toxicities deserve attention. The rate of observed myocarditis is consistent with international estimates, reiterating the importance of anticipatory cardiac surveillance, even in low-resource environments. The correlation between response to treatment and adverse events indicates that irAEs could be a marker of increased immunologic activity, although this association is exploratory in nature.

Considering the sample size, follow-up period, and heterogeneity in diagnosis limitations, the results must be interpreted cautiously. This study draws on real-world data to shed light on immune checkpoint inhibitor usage. Looking ahead, further research could involve broader patient groups, assess long-term effects, and explore factors that predict treatment response or adverse events to enhance the effectiveness of immune checkpoint therapy.

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Ethics Statement and Conflict of Interest Disclosures

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Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all the patients participants in this study. This study was approved by the Institutional Research Board and Ethics Committee.

Conflict of interest: No known conflict of interest correlated with this publication.
Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.
Competing interests: The authors declared that they have no competing interests.
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