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Characterization and Prognostic Significance of Cutaneous Immune-Related Adverse Events in Indian Patients on Immune Checkpoint Inhibitor Therapy

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ABSTRACT

Introduction: Cutaneous immune-related adverse-events (cIRAEs), commonly seen in cancer patients receiving immune checkpoint inhibitors (ICI) are reported to be associated with better patient survival; however, they have seldom been studied in Indian population. Recent reports suggest racial differences in IRAEs and also in survival outcomes.

Objectives: To study the various cIRAEs in Indian patients on ICI therapy and to analyze the association between cIRAEs and patient survival outcomes.

Methods: We conducted a retrospective cohort study of 86 cancer patients receiving immunotherapies in a tertiary care hospital in India and studied incidence, nature and grades of cutaneous immune-related adverse events and the association of cIRAEs with the patient survival outcomes.

Results: Eighty-six patients were included, of whom 16 patients (18.6%) developed cIRAEs, with pruritus (12.8%) and maculopapular eruption (8.1%) being the most common. Kaplan–Meier plot with log-rank test showed that patients developing any type of cIRAE had longer progression-free survival than those without (P = 0.023) and a better objective-response-rate (50% versus 18.5%, P = 0.008).

Conclusions: Most common cIRAEs in our study were pruritus and maculopapular rash. The incidence of cIRAEs was lower in our Indian cohort compared to that reported in Caucasian cohorts. Development of cutaneous immune-related adverse event in cancer patients on ICI was associated with a longer progression-free-survival and a better objective-response-rate. Thus, cIRAEs may serve as a surrogate marker for better patient outcomes.

Introduction

Immune checkpoint inhibitors (ICI) are a class of immunotherapeutic agents which act upon the immune check points - programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA-4), that regulate T-cell activity [1]. Under normal circumstances, immune check points protect the host cells from immune response. However, these pathways are also utilized by cancers to escape the host immunity and their inhibition results in enhancement of immune response and prevents tumor escape causing tumor destruction. This enhanced immune response is non-specific and can have collateral effects on the normal cells leading to a new spectrum of adverse events called immune-related adverse events (IRAEs). IRAEs can potentially involve any system and in severe cases can lead to treatment discontinuation or even death. Cutaneous IRAEs (cIRAEs) are one of the most common IRAEs and can have myriad presentations [2]. Since both tumor regression and IRAEs are a result of enhanced immune response, the presence of IRAEs may correlate with greater antitumor response and studies have shown that IRAEs, particularly cIRAEs may be associated with better patient survival outcomes [3–6]. However, much of the available literature on immune checkpoint inhibitors and their IRAEs is based on trials and data from Western countries and there is an inadequate representation of other populations particularly the Indian population. Reports suggest that immune checkpoint inhibitors can variation in activity and toxicity spectrum among various ethnicities such as lower incidence of IRAEs and poorer survival outcomes in Hispanics compared to Caucasian populations [7–10]. Thus, there is a need for further data on the use of ICI and various IRAEs in under-represented population groups.

In our study, we aim to study the real-world incidence and manifestations of cIRAEs seen in Indian patients on immune checkpoint inhibitor therapy and investigate the relationship between cIRAEs and patient survival.

Objectives

To study the various cIRAEs in Indian patients on ICI therapy and to analyze the association between cIRAEs and patient survival outcomes.

Methods

This was a single-institution retrospective study of patients receiving ICIs (nivolumab, pembrolizumab, atezolizumab and ipilimumab) from January 2017 to September 2021. The study was approved by the hospital institution review board. Medical records of all patients with cancers treated with at least one dose of PD-1 antibodies (nivolumab or pembrolizumab), PD-L1 antibodies (atezolizumab) or CTLA-4 antibodies (ipilimumab) during the study period were drawn from the hospital medical records database and analyzed. Information regarding patient demographics and characteristics, nature of the malignancies, ICI used, total duration of treatment, any adverse events during ICI therapy, grade of the adverse events, time till progression, time till death were retrieved from medical records. Treatments given for cutaneous adverse events and their outcomes were recorded. Wherever possible, telephonic follow-up was performed to complete missing records. Responses were assessed clinically and radiologically and classified according to standard tumor response evaluation criteria - the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and Positron Emission Tomography Response Evaluation Criteria in Solid Tumors (PERCIST) version 1.0. Adverse events during immunotherapy were documented and graded using the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. In the patients with cIRAEs, response of cIRAEs to their respective dermatological treatment was graded as no improvement, partial improvement (an improvement by one CTCAE grade) or significant improvement (an improvement by two or more CTCAE grades or improvement to grade 0). Data censoring was done in October 2021. Overall-response-rates (ORR), overall survival (OS) and progression-free-survival (PFS) were calculated and compared between patients having cutaneous adverse events and those not having cutaneous adverse events.

Tumor response was graded as complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) based on standard tumor response evaluation criteria – RECIST and PERCIST. Overall response rate (ORR) was defined as the proportion of patients who have a partial or complete response to therapy, excluding stable disease. Progression free survival (PFS) was defined as the time

elapsed since treatment initiation until disease progression or death from any cause, whichever comes first. Progression was defined as clinical worsening of the disease or radiological progression as per RECIST v 1.1 / PERCIST v 1.0 or death due to any cause. Overall survival (OS) is defined as the time as the time elapsed since treatment initiation until death from any cause. Patients were censored at the date of last follow-up if still alive at the time of the analysis.

Statistical analysis was performed using IBM SPSS version 20.0 software (SPSS Inc, Chicago, USA). Categorical variables were expressed using frequency and percentage. Continuous variables are expressed as mean ± SD or the median and interquartile range [IQR]. Chi-square test with continuity correction was used to test the statistical significance of differences in overall response rate between patients with and without adverse events. To compute the survival probability and the survival comparison between patients with and without adverse events, Kaplan–Meier analysis with log-rank test was used. Multivariable analysis of both PFS and OS was performed with Cox proportional hazard regression models. A p value of <0.05 was considered to be statistically significant.

Results

A total of 86 patients (M:F 64:22) of median age 60.5 years (IQR:18 –83) were included. This was an umbrella study comprising of multiple malignancies, with lung cancer being the most common malignancy (26 patients, 30.2%). Other common malignancies included hepatocellular carcinoma (12 patients, 13.9%), renal cell carcinoma (10 patients, 11.6%) and oropharyngeal squamous cell carcinoma (10 patients, 11.6%).

The median duration of ICI therapy was three months (IQR 2-6) with a median of five cycles (IQR 3-8.75). Fifty-one patients (59.3%) were treated with nivolumab, 29 (33.7%) with pembrolizumab, five (5.8%) with atezolizumab and one (1.2%) with combination of ipilimumab and nivolumab. Patient demographics are presented in Table 1.

A total of 42 IRAEs of any grade occurred in 28 patients (32.5%) with six patients (6.97%) having adverse events involving more than one organ system. Cutaneous (18.6%) and endocrinological adverse events (15.1%) were the most common IRAEs noted. Median time of onset of IRAEs of any type was two months. The various IRAEs are represented in Table 2.

Twenty-four cIRAEs of any grade occurred in 16 patients (18.6%) - pruritus in 11 patients (12.8%, 4 with isolated pruritus and 7 with pruritis in addition to other

Table 1. Patient Characteristics.

Clinical Characteristics	N (%)
Median age at ICI initiation	60.5 (IQR:48-71)
Gender (male)	64 (74.4%)
Cancers	
Lung cancer	26 (30.2%)
Hepatocellular carcinoma	12 (13.9%)
Renal cell carcinoma	10 (11.6%)
Oropharyngeal SCC	10 (11.6%)
Melanoma	8 (9.3%)
Hodgkin lymphoma	7 (8.1%)
Endometrial cancer	3 (3.5%)
Urothelial carcinoma	2 (2.3%)
Esophageal adenocarcinoma	2 (2.3%)
Others[a]	6 (7.2%)
ICI	
Nivolumab	51 (59.3%)
Pembrolizumab	29 (33.7%)
Atezolizumab	5 (5.8%)
Combination (Nivolumab + Ipilimumab)	1 (1.2%)
Grade of adverse events	
1	13 (15.1%)
2	20 (23.2%)
3	8 (9.3%)
4	1 (1.2%)

[a]Other cancers includes metastatic breast cancer, carcinoma stomach, pineal anaplastic astrocytoma, head and neck squamous cell carcinoma, nasal adenoid cystic carcinoma and testicular germ cell tumor accounting for 1 patient (1.2%) each.

ICI = immune checkpoint inhibitors; SCC = squamous cell carcinoma.

Table 2. Immune-Related Adverse Events (IRAEs) and their grades.

IRAE	Grade 1	Grade 2	Grade 3	Grade 4	Total
Cutaneous	9	9	6	0	24
Thyroid disorders	1	11	1	0	13
Neurological	1	0	1	0	2
Conjunctivitis	1	0	0	0	1
Diarrhea	1	0	0	0	1
Intracranial hypertension	0	0	0	1	1

cutaneous lesions), maculopapular rash in 7 (8.1%), vitiligo in 2 (2.3%) and erythema multiforme, exfoliative dermatitis, psoriasiform eruption, mucositis in one patient each (1.2%). No hair or nail changes were noted. There were 9 grade 1 cIRAEs (37.5%), 9 grade 2 events (37.5%) and 6 grade 3 events (25%). No grade 4 cIRAEs were noted. The different cIRAEs and their grades are represented in Table 3.

Of the 16 patients, ten (62.5%) received nivolumab, five (31.25%) pembrolizumab and one (6.25%) received a combination of ipilimumab and nivolumab. cIRAEs occurred after median of 2.75 months (IQR 2-3) from the initiation of ICI (median cycles of ICI: 4; IQR: 3-6).

Of the 16 patients with cIRAEs, 11 (68.75%) were managed with topicals, antihistamines or a combination of both. Four patients required systemic immunosuppression.

In addition to medical management, four patients (25%) with grade 3 maculopapular rash (2), exfoliative dermatitis (1) and erythema multiforme with mucositis (1) required an interruption in ICI therapy until the resolution of lesions. The patient with erythema multiforme developed further grade 4 complications (intracranial hypertension) and ICIs were stopped. The other patients were restarted on ICI therapy under careful observation after a drug-free period of one month. In one patient with psoriasiform eruption – Nivolumab dosing was changed from once in two weeks to once in four weeks.

Of the 15 patients treated for cIRAEs, 12 patients experienced significant improvement following treatment, one patient had partial improvement, two patients had no improvement.

Patients with IRAEs had a longer median PFS (6 months versus 3 months, P = 0.016) and a longer median OS (15 months versus 8 months, P = 0.03) compared to patients without any adverse events. ORR was also significantly higher (39.2% versus 17.2%, P = 0.02). Kaplan-Meier curves (PFS and OS) comparing patients with and without IRAEs are represented in Figure 1.

Median PFS (8 months versus 3 months, P = 0.023) and ORR (50% versus 18.5%, P = 0.008) were significantly higher in patients with cIRAEs compared to those without cIRAEs (inclusive of patients who had AEs in organs other than skin). Median OS was also longer (15 months versus 10 months). However, this association was not statistically significant (P = 0.246). Kaplan-Meier curves (PFS and OS) comparing patients with and without cIRAEs are represented in Figure 2.

Table 3. Nature and grades of Cutaneous Immune-Related Adverse Events (cIRAEs).

	No. of Patients (%)	Total cIRAEs	Nature	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous IRAEs	16 (18.6%)	24	Pruritus	5	5	1	0
			Maculopapular rash	3	2	2	0
			Vitiligo like depigmentation	1	1	0	0
			Psoriasiform eruption	0	1	0	0
			Erythroderma	0	0	1	0
			Erythema multiforme	0	0	1	0
			Mucositis	0	0	1	0

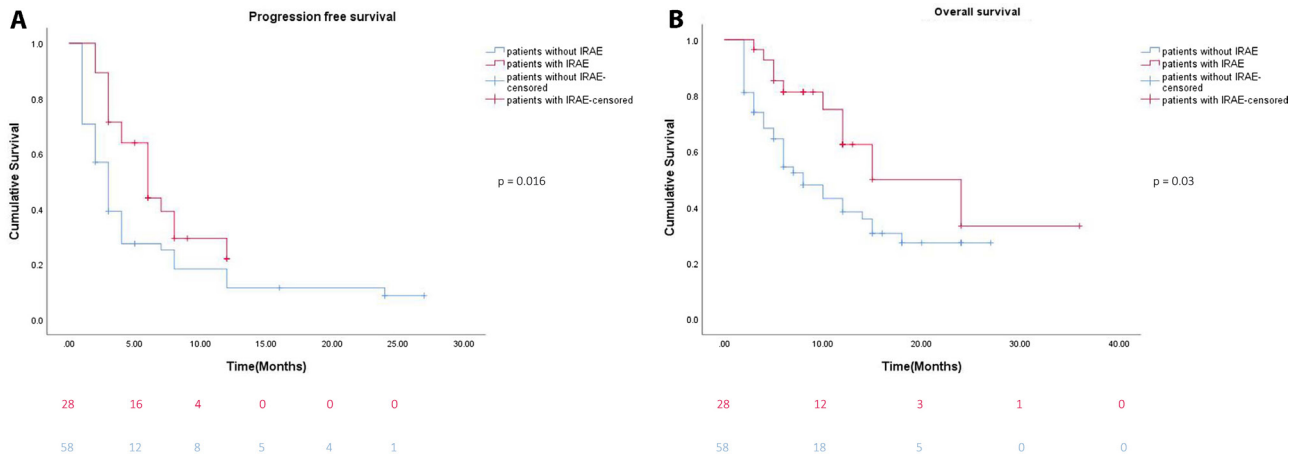

Figure 1. Kaplan Meier survival curves comparing (A) progression free survival and (B) overall survival between patients with and without immune-related adverse events (IRAEs).

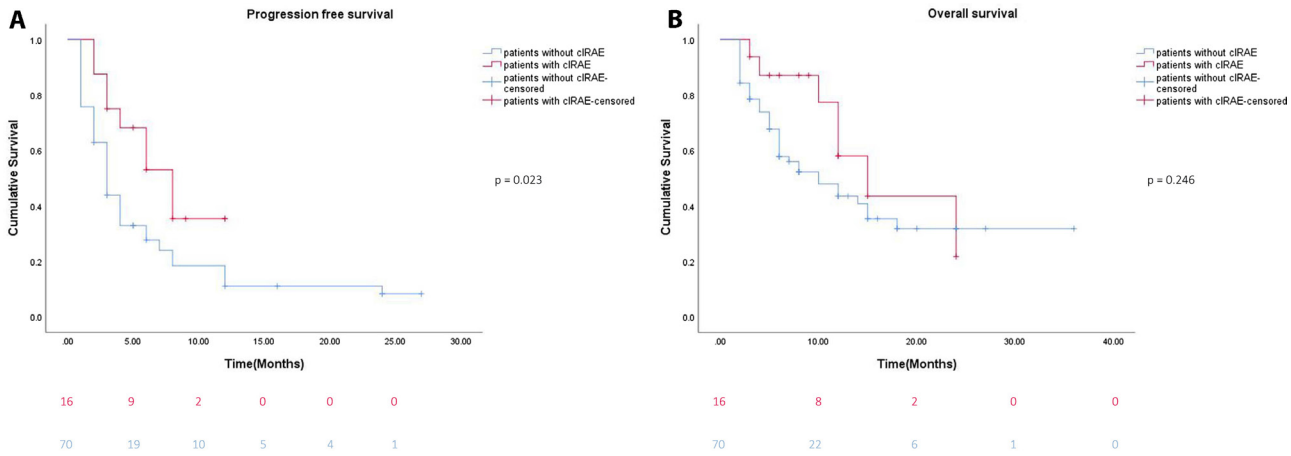

Figure 2. Kaplan Meier survival curves comparing (A) progression free survival and (B) overall survival between patients with and without cutaneous immune-related adverse events (cIRAEs).

Cox proportional hazard regression showed any IRAE (hazard ratio: 0.558, P = 0.033) and cIRAEs (hazard ratio: 0.698, P = 0.046) to have a significant association with increased PFS. Development of any IRAE was also associated with significantly increased OS (hazard ratio: 0.453, P = 0.028), whereas cIRAEs were not.

Conclusions

ICIs are effective in treating various cancers and have revolutionized cancer treatment, however, studies and trials on ICI safety and efficacy have inadequate representation of Indian population. We have conducted a real-world study characterizing the cIRAEs seen in an Indian cohort on ICI therapy. ICI response rates can be variable and reports have indicated that the presence of IRAEs maybe associated with a better therapeutic effect especially in lung cancer and malignant melanoma. Identification of predictors of ICI response are important especially in low- and mid-income countries where financial constraints and accessibility to advanced diagnostic procedures can be hurdles. We have studied the association between the presence of IRAEs and cIRAEs and treatment efficacy in terms of tumor response and survival outcomes.

The incidence rates of cIRAEs can be variable with high incidences of up-to 70% being reported in patients [11]. A recent population level analysis of cIRAEs in patients receiving ICIs in the United States has observed an incidence of 25.1% [12]. Similar incidence has been observed in a large Taiwanese cohort (27.4%) [13]. Compared to this, we observed a relatively lower incidence of cIRAEs (18.6%).

With regard to the individual types of cIRAEs, the majority noted in our study were pruritus and maculopapular rash similar to prior literature focusing on ICI associated cutaneous reactions [13–15]. Vitiligo like depigmentation has been commonly reported in melanoma patients treated with ICI [16]. This was also seen in our study, in two patients with malignant melanoma. Though other studies have reported adverse events like bullous pemphigoid, lichenoid eruption, acneiform eruptions, neutrophilic disorders and sarcoid like lesions, we did not see any such reactions. We also did not encounter any SCARs like SJS/TEN, DRESS and AGEP that have been reported in other studies [17].

cIRAEs occurred at a median duration of 2.75 months after initiation of ICI therapy whereas other IRAEs (other than skin) occurred earlier (median duration: 2 months).

In a previous study on the characteristics of cIRAEs and non-cutaneous IRAEs, cIRAEs were found to precede and increase the risk of other organ involvement in the same patient on ICI therapy [18]. In our study, of the six patients who developed both cutaneous and non-cutaneous IRAEs, only two patients had cutaneous involvement prior to the extracutaneous adverse events, whereas it was the reverse in the other four.

cIRAEs were well tolerated. The majority of the cutaneous toxicities were mild and were managed with topicals and antihistamines. Grade 1 and 2 cIRAEs formed 75 % of the total. Grade 4 dermatological IRAEs –were not seen in our cohort.

Of the 15, 14 had improvement in their symptoms with 13 having significant improvement (fall of two grades or fall to grade 0). One patient with psoriasiform eruption had only moderate improvement – however, this patient was not treated with any immunomodulatory agents. Two patients with vitiligo like depigmentation did not request any treatment. However, these patients had only grade 1 and grade 2 vitiligo like depigmentation with limited area of involvement. one of these patients had associated pruritus which was treated with antihistamines.

The occurrence of any IRAE was associated with a higher ORR and a longer PFS and OS. Thus, the appearance of any IRAE in itself may be an indicator of better patient survival, similar to findings reported in other studies [3,19]. Patients

with any cIRAEs had a significantly longer median PFS and a higher ORR. Multivariable analysis also showed cIRAEs to be associated with a longer PFS. They were also associated with a longer OS; however, it was not statistically significant. This is in contrast with other studies where in cIRAEs were associated with better survival outcomes with regard to both PFS and OS [4,20–22].

Limitations of the study are its retrospective design and small sample size. Six out of the 16 patients with cutaneous IRAEs also had other organ IRAEs which may be a confounding factor.

In conclusion, pruritus and maculopapular rash were the most common cIRAEs seen in our study of Indian patients on ICI therapy which is similar to the profile of cIRAEs seen in other populations. However, the incidence of cIRAEs was lower. cIRAEs were found to be associated with a superior ORR and PFS. Compared to adverse events in other organ systems, cutaneous adverse events are readily evident on a simple physical examination and do not usually require any investigations. Thus, cIRAEs may serve as an easily accessible and actional clinical surrogate marker for predicting the tumor response. This can especially be important in resource poor settings.

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