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Original Article

A Multicenter Study on the Challenges and Real-World Utilization of Immune Checkpoint Inhibitors in Resource-Constrained Settings: Insights and Implications from India

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Abstract

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Using immune checkpoint inhibitors (ICIs) has revolutionized cancer treatment, but access and affordability remain significant challenges, particularly in resource-constrained settings. This multicenter study evaluated the utilization, outcomes, and challenges associated with ICIs in India. Data from multiple centers involving patients treated between January 2018 and December 2021 were retrospectively collected. Patient demographics, treatment indications, biomarker testing, financial coverage, toxicity, treatment discontinuation, clinical benefit, progression-free survival (PFS), and overall survival (OS) were analyzed. Ninety-one patients were analyzed; lung cancer (39.6%) and renal cancer (11%) were the main indications for ICI use. Programmed death ligand 1 expression was tested in 40.7% and tumor mutational burden in 3.3%. Financial constraints influenced 41.8% of patients with out-of-pocket expenses. Treatment discontinuation due to financial constraints occurred in 17.6%, with 50% showing ongoing responses. The median number of cycles was 4; the median PFS was

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Keywords
- biomarker testing
- checkpoint inhibitors
- immunotherapy
- resource-constrained settings
- optimization

4.6 months, and the median OS was 15.4 months. The lung cancer cohort had a median PFS of 5.7 months and a 1-year OS of 57.6%. Limited biomarker testing and 6.6% grade ¾ toxicities were observed. This study revealed challenges in ICI utilization in resource-constrained settings driven by financial constraints. Compared with prior studies, improved outcomes reflect better patient selection and evolving understanding of ICI use. However, in the absence of biosimilars, cost remains a significant barrier. Solutions to increase access include using lower doses, which may be as effective.

Introduction

Amid the evolving landscape of cancer immunotherapy and considering the issues faced in managing patients with financial constraints being managed at government and private teaching centers, this study aimed to harness real-world data from a multicenter research network to comprehensively assess the utilization, indications, and outcomes of immune checkpoint inhibitors (ICIs) in Indian patients, addressing the scarcity of such insights from the region.

Materials and Methods

The Network of Oncology Clinical Trials India (NOCI) accessible at www.noci-india.com is a cooperative research network developed with a grant from the Department of Biotechnology, Govt. of India, having six member institutes from all parts of the country. Electronic and paper databases from these institutes were checked from January 1, 2018 to December 31, 2021, and data on the cases receiving at least one ICI cycle was collected. Progression-free survival (PFS) was calculated from the date of the first cycle of ICI till the documented date of progression or last cycle of ICI or death, whichever was earlier. Overall survival (OS) was calculated from the date of the first cycle of ICI till the date of death or last follow-up. Data was censored at the last follow-up before December 31, 2021, for patients on treatment or follow-up. The objective response rate was calculated based on the best responses per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Toxicity data was captured per the documented events and graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.02. After obtaining ethics committee approval from each center, including waiver of consent, retrospective data was collected from the records.

Analysis

Descriptive statistics was used for demographic data. Response rate and side-effects were calculated in percentages. Data was collected in an Excel sheet, which was later cleaned, coded, and analyzed with SPSS software 22. Time-to-event analysis was plotted on Kaplan–Meier curves, and OS and PFS data were calculated. Cox regression was used to calculate the hazard ratio. Univariate analysis was done using the Log-rank test, and multivariate analysis was done using Cox regression. *p*-Value less than 0.05 was considered significant.

Results

Ninety-one patients (males: 75.7%; median age: 61 years [30–81]) were analyzed (►**Supplementary Table S1**, available in the online version). The most common indication for ICI use was lung cancer (39.6%), followed by renal cancer (11%). Programmed death ligand 1 (PD-L1) expression was tested in 40.7%, and tumor mutational burden (TMB) was checked only in 3.3%. Anti-PD-1 agents (pembrolizumab and nivolumab) were used in most cases (74.7%). Most patients received ICI in the third line and beyond (42.9%), and single-agent use of ICI accounted for 59.3%. In terms of financial coverage, out-of-pocket expenses accounted for 41.8%, followed by government-assisted schemes at 36.3%. The toxicity profile and reasons for discontinuation of therapy are described in ►**Supplementary Table S2**, available in the online version. The majority of the cases did not have documented toxicities (86.6%), and grade ¾ toxicity was seen in 6.6%.

Eighty of ninety-one (87%) patients discontinued ICIs at the time of analysis. The median number of cycles was 4 (1–44). Disease progression ($n = 53/91$ [58.2%] and financial constraints ($n = 16/91$ [17.6%]) were the most common indications for stopping ICI. Of those who had stopped ICI due to financial constraints, 50% had an ongoing response (CR + PR + SD) at the time of stopping. Clinical benefit (CR [6.6%] + PR [12.1%] + SD [29.6%]) was seen in 48.3%. After a median follow-up of 6.4 months, the median PFS was 4.6 months (95% confidence interval [CI]: 2.01–7.18), and the median OS was 15.4 months (95% CI: −7.32–23.4) for the whole cohort (►**Fig. 1**). The median PFS for the lung cancer cohort was 5.7 months (95% CI: −0.7–10.5). The median OS was not reached in lung cancer, and the 1-year OS for lung cancer was 56.7%.

Discussion

In this multicenter series on the use of ICIs from India, the responses and outcomes were comparable to those real-world data reported in literatures.[1–4] Financial constraints were the major factor limiting the use if ICIs. This was

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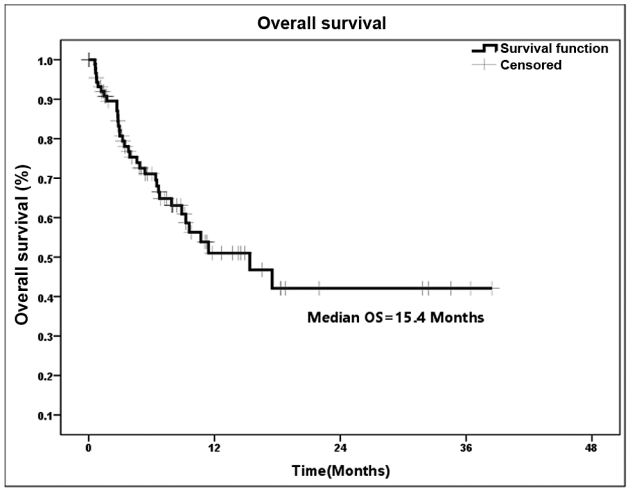

Fig. 1 Overall survival for whole cohort.

reflected in the high rate of discontinuation for financial reasons. The median number of cycles was 4 (1–44), having median PFS of 4.6 months and median OS of 15.4 months. The survival may be marginally improved when compared with previous single-center Indian studies.[1,3] The improvement in PFS and OS could be due to the fact that by the time this study was done, the indications and understanding how to use ICI had improved and patient selection also might have been better.

All patients in this cohort received the standard ICI doses of pembrolizumab at 200 mg once in every 3 weeks, nivolumab at 3mg/kg once in every 2 weeks or 240 mg intravenous (IV) once in 2 weeks, and atezolizumab at 1,200 mg IV every 3 weeks. The most common indication for using ICI was lung carcinoma, where the median PFS was 5.7 months (1-year OS of 57.6%). As most patients received ICI in the third line and beyond (42.9%), the outcomes may be slightly lesser than those studies in which ICI was used upfront.

While upfront use of ICI has significant financial burdens and fewer patients would opt for ICI in later settings, the disease burden and performance status in these patients may be limiting factors. This could also explain the use of single-agent ICI in 59.3%. As most patients received the ICI agents at third line and beyond, this justifies the limited PD-L1 testing. This could also be attributed to the fact that PD-L1 testing is not mandated in patients having renal cell carcinoma,[5–7] urothelial carcinoma,[8] melanoma,[9] and beyond the first line in lung cancer[10] and head and neck cancers.[11] With regard to biomarkers testing for ICI use, which is still evolving, the surrogate markers PD-L1 and TMB were tested only in 40.7 and 3.3%, respectively. The cost of biomarker testing for PD-L1 depends on the platform used and ranges between Rs 12,000 and Rs 15,000, but patient assistance programs (PAP) are available. Testing for TMB is much more expensive (Rs. 1,50,000–Rs 300,000) and hence was done only in very few patients. The PD-L1 cutoffs and platforms for testing were heterogeneous and hence varied across different disease subtypes. Being a retrospective study, only higher-grade toxicities are likely represented in the records. Grade ¾ toxicities accounted for 6% (details in ►**Supplementary Table S3**, available in the online version). Regarding financial support, which plays a significant role in resource-constrained settings, most patients (41.8%) had out-of-pocket expenses. This could have been a major limiting factor as 17.6% stopped treatment due to financial constraints, and among those who stopped treatment because of cost, 50% had an ongoing response at the time of discontinuation. Cost is an important limiting factor for the use of ICIs in India. In a study from Tata Memorial Hospital, only 151 received ICI among 9,651 (1.5%) who were offered ICI.[1] The approximate cost of different checkpoint inhibitors for Drugs Controller General of India (DCGI)-approved indications with PAP per cycle is about Rs 2,10,000 for pembrolizumab (200 mg every 3 weeks), Rs 1,30,000 for atezolizumab (1200 mg, every 3 weeks), and Rs 1,20,000 for nivolumab (240 mg every 2 weeks). Possible solutions could be to generate more data on the use of lower dose ICIs and extended interval dosing of these agents.

Despite the limitations of a retrospective study representing a heterogeneous group of cancers, this study highlighted the practical challenges to the use of ICIs in the Indian context.

Conclusion

This multicenter study highlighted the challenges of using ICIs in resource-constrained settings and emphasized the urgent need for affordable access through the development of biosimilars and dose optimization studies. It provides practical insights into ICI utilization from different centers across India, offering a comprehensive understanding of the real-world scenario.

Note

Clinical Trials Registry-India (CTRI) Number: CTRI/2022/01/039233.

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Conflict of Interest

None declared.

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