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Immune checkpoint inhibitors in patients with solid tumors and poor performance status

A prospective data from the real-world settings

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Abstract

Immune checkpoint inhibitors (ICIs) are rapidly being incorporated as treatment option either alone or in combination with chemotherapy in most of the solid tumors. Since there is very limited data of ICI in patients with poor performance status (PS) from the real world settings, we performed a retrospective audit of patients who received ICI and report the analysis based on ECOG PS of these patients.

This study is a retrospective audit of a prospectively collected database of patients receiving ICIs for advanced solid tumors in any line between August 2015 and November 2018 at Tata Memorial Hospital, Mumbai, India. All statistical calculations were performed using SPSS statistical software for windows version 20.0.

A total of 155 patients who received ICIs during the specified period were evaluated for this study. Baseline ECOG PS 0–1 (n = 103, 66.4%) patients was associated with median OS 9.1 (95% CI [confidence interval], 4.4-NR) months when compared to ECOG 2–4 (n = 52, 33.5%) which had a median OS of 2.9 (95% CI; 1.8–5.5) months (HR, 1.7, 95% CI, 1.1–2.7, log rank $P = .017$). The disease control rate for the poor PS group was 34.6%. However, 27.3% patients (95% CI: 20.3–34.3) were still alive at 1 year. Median OS in patients with PS 2 was 3.7 months (95% CI: 0–11.6) as compared to 1.8 months (95% CI: 0.2–3.4) for those with PS 3–4 (HR-2.0; 95% CI: 1.0–3.9, $P = .041$). The tolerance to ICIs was good with no grade 3/4 toxicities in 44 (84.6%) patients.

Immune checkpoint inhibitors are a safe and effective therapeutic option even in solid tumor patients with poor performance status.

Abbreviations: CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, ICI = immune checkpoint inhibitor, irAEs = immune-related adverse effects, NR = not reached, NSCLC = non-small cell lung cancer, PS = performance status.

Keywords: checkpoint inhibitor, poor performance status, real world data, survival

1. Introduction

Immune checkpoint inhibitors (ICIs) are rapidly being incorporated as treatment option either alone or in combination with chemotherapy in most of the solid tumors. However, it is clear from the available data that only a proportion of the patients respond favorably to the immunotherapy and the rest progress

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All authors provide their consent for publication of this manuscript. The participants provided informed consent for enrollment in the prospective database.

The data (with removal of patient identification) can be made available on reasonable request to the corresponding author.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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and succumb to the disease.[1] The search for an appropriate biomarker for identifying suitable patients for ICI continues. Some of these biomarkers include expression of PD-L1, microsatellite stability, tumor mutation burden (TMB), and tumor-infiltrating lymphocytes.[2] Apart from these laboratory markers, various clinicopathological features have been investigated for their possible role as predictors of response to ICI; these include gender, age, family history, and addiction.[3–6] These factors act possibly by modulating an individual's immune response and, thus, bearing on treatment outcomes and response to ICI. Besides, another important factor that is used by physicians on a daily basis to decide the intensity of therapy is performance status (PS) of the patient; the Eastern Cooperative Oncology Group (ECOG) scale is the most commonly used worldwide for the same.

Modern treatment is guided by evidence-based-medicine, which relies mostly on randomized controlled trials and meta-analysis. However, an important drawback of this approach is that data may not be available for all the clinical situations, and it might lead to over or under-expression of the benefit of the therapy in real-world settings. One such scenario is the management of cancer patients with poor PS. These patients are underrepresented in clinical trials as most of the trials have exclusion criteria of ECOG PS $>$ 2, or even PS $>$ 1. Besides, ECOG PS seems to corroborate with the immune function, and there is evidence that T-lymphocyte subpopulation (CD8+ and CD4+ T-cells) can reflect the PS in gastric cancer patients.[7] In a real-world scenario, a patient who is frail or has poor PS is usually offered supportive care alone unless there is a correctable cause of poor PS. However, with the advent of immunotherapy, patients who are otherwise deemed unfit to receive cytotoxic chemotherapy agents are also offered ICIs due to their good tolerance. Thus, studies from real-world settings become important to have a clue about the best possible approach in such situations. Thus, we performed a retrospective audit of patients who received ICI and report the analysis based on ECOG PS of these patients. The primary objective of this study was to find the clinical outcomes of patients having solid tumors with poor PS and to identify the factors which predicted the outcomes.

2. Patients and methods

2.1. Study population and intervention

This study is a retrospective audit of a prospectively collected database of consecutive patients receiving ICIs for advanced solid tumors in any line between August 2015 and November 2018 at Tata Memorial Hospital, Mumbai, India. Besides the regular demographic data, baseline ECOG PS data was obtained and confirmed from electronic medical records. Also, the data on the use of antibiotics (considered significant if used for 5 days or more) and steroids was obtained from electronic medical records. Steroid use was considered significant if patients received prednisolone equivalent of ≥10 mg per day for any duration between 2 weeks before the start of ICI and concomitantly with ICI. PD-L1 testing was not done, as most of the patients received nivolumab therapy in the second-line or beyond. Patients received nivolumab at a dose of 3 mg per kilogram or flat 240 mg every 2 weeks or pembrolizumab 200 mg 3 weekly. The treatment was continued until disease progression or unacceptable toxicities. The study was approved by the institutional review board and ethics committee. The study was conducted as per the Declaration of Helsinki and local guidelines of the Indian Council of Medical Research, New Delhi, India.

2.2. Clinical outcomes

Response assessment was performed by using the standard institutional radiological evaluation protocol every 8 to 12 weeks or any symptoms/signs of clinical progression as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events during immunotherapy were documented and graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.02. Progression free survival (PFS) was defined as the time duration between the start of ICI until the date of progression or death due to any cause, or the last follow-up date, whichever was earlier. The overall survival was calculated from the date of starting of ICI to the date of death. The patients who were alive at the date of the last contact were censored. Disease control was defined as absence of progression and included patients with complete or partial response and stable disease.

2.3. Statistical analysis

To summarize categorical and continuous variables, descriptive statistics were used. The Kaplan–Meier estimator was used for time-to-event analysis, while the Cox proportional model was used to calculate the hazard ratio. P value (two-sided) $<.05$ was considered statistically significant and all confidence intervals (CI) were calculated at the 95% level. SPSS statistical software for windows version 20.0 (Armonk, New York, IBM Corp.) was used for all statistical calculations.

3. Results

A total of 155 patients who received ICIs for the treatment of solid tumors in the palliative setting during the specified period were evaluated. The performance status as per ECOG was 0–1 in 103 (66.4%) patients, while 52 (33.5%) had poor PS (ECOG 2–4). Baseline performance status ECOG 0–1 was associated with median OS 9.1 (95% CI, 4.4-NR) months when compared to ECOG 2–4 which had a median OS of 2.9 (95% CI, 1.8–5.5) months (HR, 1.7, 95% CI, 1.1–2.7, log rank $P=.017$). Further study reports the analysis performed on the poor PS subgroup (n = 52). Figure 1 shows the flow diagram of the study. The median age of the patients with poor PS who received ICIs was 59.4 (range 36–83) years, and 34 (65.4%) patients were males, rest (34.6%) were females; 36 (69.2%) had comorbidities with hypertension (HTN) in 17 (40.4%), diabetes (DM) in 20 (38.4%) patients, and 5 (9.6%) had both DM and HTN. Out of 52 patients, 50 (96.1%) received nivolumab while rest 2 (3.9%) patients received pembrolizumab as single-agent therapy. ICI was used as first or second-line therapy in 34 (65.4%) patients while rest 18 (34.6%) received in the third line or beyond. Nine (17.3%) patients were diagnosed to have brain metastasis at the time of initiating ICI. The primary site was lung in 32 (61.5%) patients (with histology being non-small cell lung cancer in all patients), head and neck 8 (15.4%), and others in 12 (23.1%) patients. Thirty two (61.5%) had body mass index of less than 25 kg/m^2, 33 (63.4%) patients received antibiotics while 15 (28.8%) received steroids (prednisolone equivalent 10 mg or more). The median duration of antibiotic use was 10 (5–40) days.

The median duration of follow up was 9.8 months (95% CI: 7.7–11.8). Out of 52 patients, 6 (11.5%) had partial response, 12

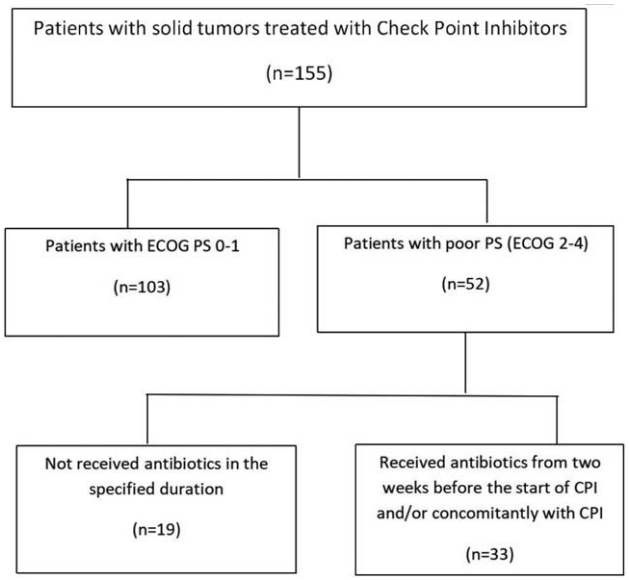

Figure 1. Consort diagram of the study.

(23.1%) stable disease, 20 (38.5%) progressive disease while 14 (26.9%) patients were not evaluable as response scan was not available. Thus, the disease control rate was 34.6% with 27.3% of patients (95% CI: 20.3–34.3) were still alive at 1 year (Fig. 2). Table 1 shows the results of the Cox-regression analysis of various factors in the study patients. The only factor which differentiated the outcomes was PS of 2 vs 3–4. Median PFS in patients with PS 2 was 2.6 months (95% CI: 0.5–4.6) as against 1.2 months (95% CI: 0.4–2.0) for patients with PS 3–4 (HR 2.2, 95% CI: 1.1–4.2, $P = .013$). PFS at 6 months was 35.9% (±9.1) vs 9.1% (±6.1), respectively. Median OS in patients with PS 2 was 3.7 months (95% CI: 0–11.6) as compared to 1.8 months (95% CI: 0.2–3.4) for those with PS 3–4 (HR-2.0; 95%CI: 1.0–3.9, $P = .041$, Fig. 3). Survival at 12 months for patients with PS 2 was 35.4% (95% CI: 25.7–45.1) vs 17.7% (95% CI: 8.9–26.5) for patients with PS 3–4. Among the patients who received antibiotics, median OS for patients who received ≤10 days of antibiotics was 1.8 months (95% CI: 1.3–2.5), while for patients receiving >10 days of antibiotics, it was 1.9 months (95% CI: 1.8–2.1), $P = .886$. The median OS of lung cancer patients (n = 32) was 1.9 months (95% CI: 1.0–2.8) with 1-year survival being 29.4% (95% CI: 20.9–37.9). There was no significant difference in survival on the basis of the use of steroids and antibiotics, gender, age, site of primary, line of therapy, body mass index, development of immune-related adverse effects (irAEs), and presence of brain metastasis.

The tolerance to ICI was good, with no grade 3/4 toxicities in 44 (84.6%) patients. The most common toxicity was fatigue in 8 (15.4%), anorexia 6 (11.5%), and skin rash in 4 (7.7%) patients. Grade 3/4 toxicities included pneumonitis in 3 (5.7%), hepatitis and hyponatremia, each in 2 (3.8%), and colitis in 1 (1.9%) patient. Further ICI was withdrawn in 4 (7.7%) patients due to toxicities.

4. Discussion

Data from both retrospective studies and subgroup analysis of prospective trials support the notion that poor PS patients do not

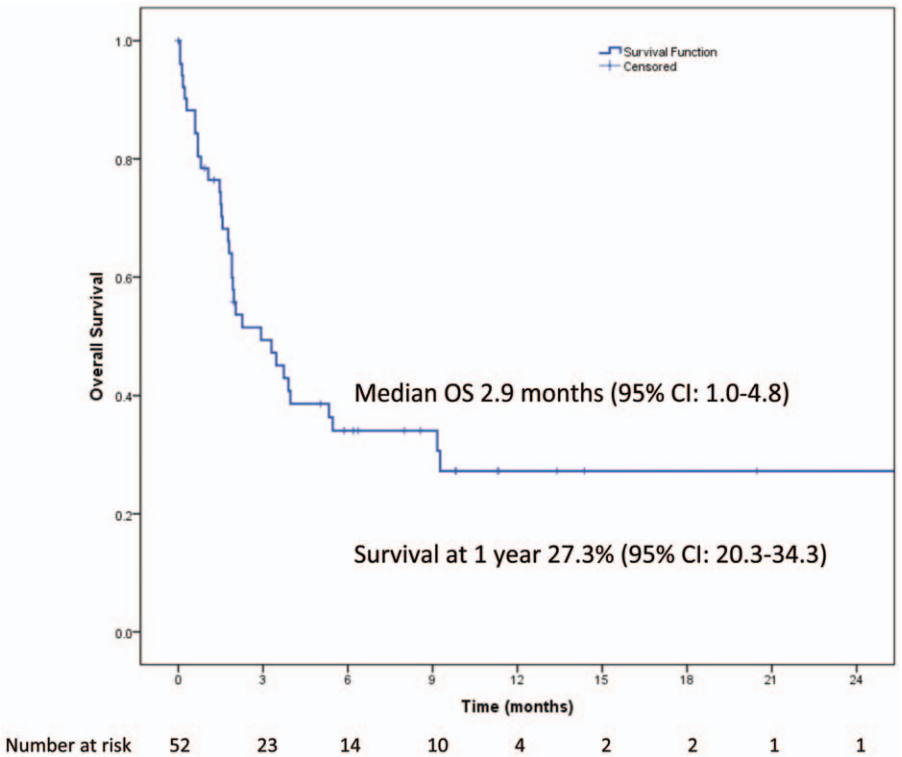

Figure 2. Kaplan–Meier survival curve showing the overall survival for the patients with poor PS (ECOG PS 2-4). Though the median survival was 2.9 months, 27.3% patients survived more than a year.

Table 1

Cox regression analysis of factors in the study patients with baseline ECOG performance score of ≥2.

Factor	Subfactors	n (%)	Median OS (95% CI)	*P* value
Gender	Female	18 (34.6)	1.9 (1.7–2.0)	.523
	Male	34 (65.4)	4.4 (2.4–6.4)	
ECOG PS	2	29 (55.7)	3.7 (0–11.6)	.041
	3–4	23 (44.3)	1.8 (0.2–3.4)	
Line of therapy	1–2	34 (65.4)	3.7 (0.9–6.5)	.614
	3 or more	18 (34.6)	1.9 (1.6–2.1)	
Age	<60 years	28 (53.8)	1.9 (1.7–2.1)	.106
	≥60 years	24 (46.2)	5.4 (0–11.5)	
Brain metastasis	No	43 (82.7)	3.4 (1.3–5.6)	.311
	Yes	09 (13.3)	1.9 (0–4.3)	
Antibiotics Use	No	19 (36.5)	9.2 (0–19.6)	.162
	Yes	33 (63.5)	1.9 (1.7–2.2)	
Steroids Use	No	37 (71.1)	3.3 (1.4–5.2)	.560
	Yes	15 (28.9)	1.9 (1.6–2.1)	
Site of primary	Head and neck	08 (15.4)	3.3 (0.6–6.0)	.692
	Lung	32 (61.5)	1.9 (1.0–2.8)	
	Others	12 (23.1)	5.3 (1.0–4.8)	
Body mass index (kg/m^2)	<25	32 (64.0)	2.2 (0.4–4.1)	.198
	≥25	18 (16.0)	3.9 (0–9.6)	
irAEs	No	42 (80.8)	2.2 (0.8–3.7)	.518
	Yes	10 (19.2)	9.2 (1.2–17.1)	

CI =confidence interval, ECOG PS = Eastern Cooperative Oncology Group Performance Score, HR = hazard ratio, irAEs = immune-related adverse effects, NR = not reached, OS = overall survival.

benefit from palliative chemotherapy, and cytotoxic therapy will lead to further deterioration in the quality of life precluding meaningful survival benefit.[8] In our study, survival at 12 months was 27.3% (for PS 2, 35.4%, and 17.7% for patients with PS 3–4). For NSCLC, 1-year survival in our study was 29.4%. This compares favorably to PS 2 patients of NSCLC treated by chemotherapy having 1-year survival of around 20%.[9] Middleton et al reported PePS2 study results in abstract form in which pembrolizumab was given to PS 2 patients of NSCLC; durable clinical benefit (complete or partial response or stable

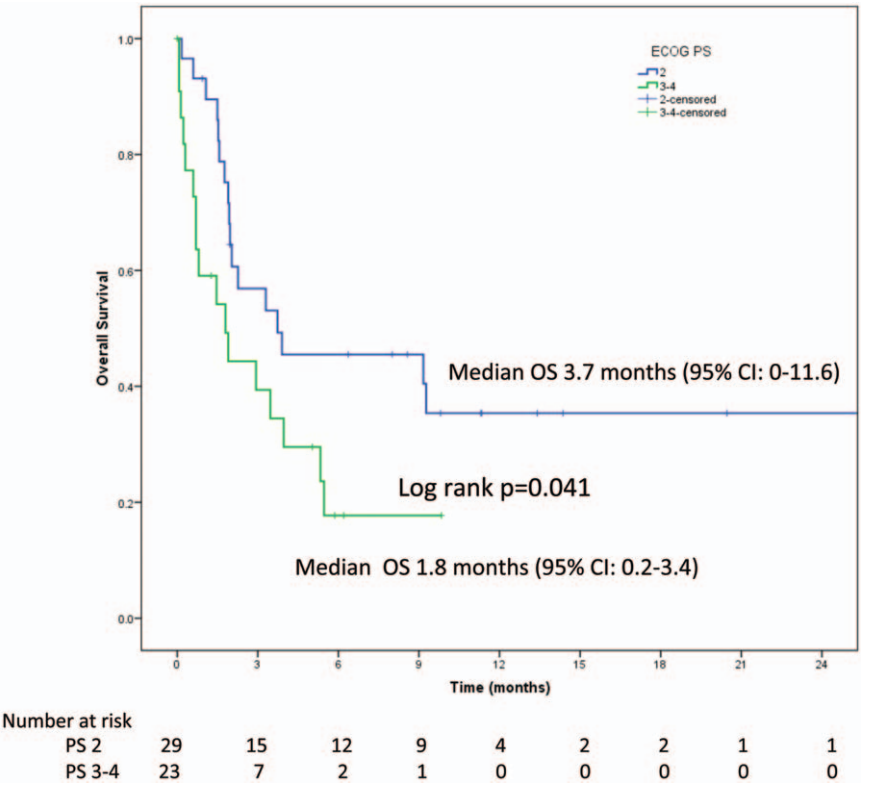

Figure 3. Kaplan–Meier curve showing overall survival in patients on immune checkpoint inhibitors with ECOF performance score 2 (blue) vs 3–4 (green).

disease at 18 weeks) was reported to be 33%.[10] They concluded that pembrolizumab is a safe and effective therapy for this category of patients. Our results also show that poor PS patients can be safely exposed to ICIs without excess toxicities. This is especially important as poor PS patients are expected to experience severe adverse effects of cytotoxic treatment and are not considered for such therapy and offered supportive care alone. ICIs appear to be a viable option in such a situation as ICIs are expected to have low adverse effects.

Wong et al reported inferior outcomes of metastatic melanoma patients with PS 2–3 treated with ICI, with median OS for PS 0–1 19.5 months vs 1.8 months for PS 2–3 ($P < .001$).[11] On the contrary, a meta-analysis by Bersanelli et al found that ICIs improved survival regardless of the ECOG PS status of the patient.[12] It should be noted that the groups compared in this study were PS 0 vs PS 1–2 with a very small number of PS 2 patients. In another study, the OS was significantly different between Italian patients of NSCLC with PS 0 and 1, and also PS 1 and 2 receiving nivolumab under an expanded access program.[13] In our study also, we found OS to be significantly different between PS 2 and PS 3–4, which underline the importance of PS as a prognostic factor.

In a meta-analysis by Dall'Olio et al, ECOG PS ≥ 2 was found to be an important prognostic factor for chemotherapy in NSCLC.[14] However, it should be noted that there was a high level of heterogeneity for both OS and PFS analysis. This might be explained by patient heterogeneity within the PS 2 population and also, the subjectivity associated with ECOG PS assessment. Bonomi et al generated a predictive survival model was generated for patients of advanced head and neck squamous cell cancers treated by ICIs.[15] ECOG PS of 2 or 3 predicted significantly inferior PFS and OS with HR of 4.66 (95% CI 2.78–7.80, $P < .001$) for OS as compared to PS of 1. These data are in concordance with the results reported in the present study.

This study's important limitations include the retrospective nature and the cohort of NSCLC and head neck cancer patients, which may not apply to all the solid tumors treated with ICI. Also, the small sample size of the patients is an important drawback for this study as this precludes reaching a definite conclusion. Despite these limitations, this study reports data from real-world settings on ICIs use in poor PS patients.

5. Conclusions

Immune checkpoint inhibitors are a safe and effective therapeutic option even in solid tumor patients with poor performance status. This needs further study in a larger sample size to reach a firm conclusion.

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Author contributions

Conceptualization: Vanita Noronha, Vijay M Patil, Kumar Prabhash.
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Writing – original draft: Akhil Kapoor.
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