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Efficacy and Safety of Low-Dose Nivolumab in Treatment of Advanced Solid Tumors: A Retrospective Audit from Resource-Constrained Settings

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Abstract

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Background Immunotherapy has improved outcomes in many advanced solid tumors. In resource-constrained settings, less than 2% of patients can afford standard dose immunotherapy. A recent phase II study showed the efficacy of low-dose immunotherapy in this setting. We used low-dose immunotherapy on a compassionate basis in patients who had progressed on available standard treatment options and standard dose immunotherapy was not feasible.

Patients and Methods We retrospectively collected data from the medical oncology department for consecutive patients who had initially received standard lines of therapy followed by low-dose immunotherapy (nivolumab 40 mg) on a compassionate basis. The demographic details, histology, prior treatment, clinical and radiological response, date of disease progression, date of death, and toxicity data were collected.

Results A total of 54 consecutive patients, who received low-dose immunotherapy with nivolumab from January 1, 2018 to February 14, 2020, were included in this analysis; 4 patients were not radiologically evaluable. The median age was 50.4 years (range 35–74 years), male:female ratio was 6:1. The most common comorbidities were hypertension and diabetes seen in 12 (22.2%) and 6 (11.1%) patients, respectively. The majority of the patients (70.4%) were of head and neck cancer. The median follow-up was 4.5 months (range 0.5–11.7). Clinical benefit was observed in 18 (33.3%) patients.

Keywords

- low-dose immunotherapy
- nivolumab
- resource-constrained settings
- solid tumor

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Partial response and stable disease were achieved in 9 (16.7%) and 5 (9.3%) patients, respectively. Median survival was not reached for these patients. Six months progression-free survival and overall survival were 100 versus 8.7% (hazard ratio [HR] 0.05, 95% confidence interval [CI]: 0.01–0.36; $p = 0.003$) and 100 versus 29.7% (HR 0.03, 95% CI: 0.00–0.95; $p = 0.047$), respectively, for responders and nonresponders. The side effects were manageable.

Conclusion In resource-constrained settings, low-dose immunotherapy with nivolumab seems to be an effective treatment option. Further studies are warranted to evaluate this approach.

Introduction

Immune checkpoint inhibitors (ICIs) have provided long-term disease control in palliative settings in advanced solid cancers with minimal toxicities. They may be either blocking programmed death 1 (PD-1) or PD-ligand 1 (PD-L1).[1] Nivolumab and pembrolizumab, anti-PD-1 antibodies, have become an important treatment option for metastatic disease.[2,3]

The dose of chemotherapy depends on the maximum tolerable dose at which the maximal efficacy can be harnessed but this concept does not apply to immunotherapy. Their mechanism of action, efficacy, and safety is quite distinct from molecular-targeted agents and chemotherapy, which acts on different cell cycle phases. ICIs influence T-cells to selectively identify cancer cells and indirectly potentiate their attack on cancer cells.[4]

ICIs have shown no correlation between dose and efficacy or dose and toxicity in initial phase I trials. The studies were not able to recognize the maximal tolerated dose (MTD) for nivolumab and at various dose levels ranging from 0.1 to 10 mg/kg, there is no difference in safety profile.[5,6] So, the dose and interval for nivolumab were defined arbitrarily without considering MTD. Similarly, the antitumor activity for pembrolizumab was observed at doses ranging from 1 to 10 mg/kg and intervals (either every 2 or 3 weeks).[7,8] Based on the pharmacokinetic data, the Food and Drug Administration (FDA) approved the pembrolizumab dose of 2 mg/kg initially followed by 200 and 400 mg fixed dose and nivolumab dose of 3 mg/kg and then 240 and 480 mg fixed dose.[9]

In resource-constrained settings, less than 2% eligible cancer patients are able to afford ICI.[10] Low-dose immunotherapy is an attractive concept in this settings.[10] The concept emphasizes the shift toward using biologically effective doses (BEDs) rather than the MTDs derived from phase I studies as BED is generally much lower than MTD in targeted/immunotherapeutic agents.[11] The concept of BED is that antibodies and targeted therapies have a dose level, above which the dose–response curve plateaus, and it is frequently below the MTD. The use of BED instead of MTD puts patients at lower risk of toxicity and is more cost-effective.[11] This study intended to evaluate the efficacy and safety of low-dose nivolumab in palliative settings.

Patients and Methods

We retrospectively collected data from the medical oncology department for patients who had received initially standard lines of therapy and on progression planned for low-dose immunotherapy with nivolumab 40 mg every 2 or 3 weekly from January 1, 2018 to February 14, 2020. The demographic details including age, sex, residence, site of disease, histology, prior treatment, clinical and radiological response, date of disease progression, date of change in treatment, further treatment, date of death, and toxicity data were collected.

The patients who were candidates of immunotherapy but cannot afford the high cost were treated with the low dose after explaining the treatment and written informed consent was taken from each of the patient prior to starting of the therapy as per the institutional standards. The treatment was continued until disease progression, logistic issues mainly financial that restricted continuing ICIs, or death. The patients were continued on treatment if they were having a clinical response according to clinician's assessment.

Response Evaluation

The patients underwent chest and abdomen computed tomography scans every 2 to 3 months as per the institution protocol, and further as needed for response evaluation except in cases of obvious clinical progression. Response Evaluation Criteria in Solid Tumors (RECIST V. 1.1) was used to assess the systemic response.[12] Patients were stamped as responders, if there was clear RECIST 1.1 partial response.

Statistical Analyses

Progression-free survival (PFS) was calculated from the date of start of the nivolumab until progression or death due to any cause. Overall survival (OS) was calculated from the date of start of nivolumab until death due to any cause, or the last follow-up date. Patients were censored at the date of their last follow-up.

The baseline characteristics and clinicopathological findings of patients and response rates were analyzed by descriptive statistics. The comparisons were done using the chi-square test or Fisher's exact test where appropriate. Survival analyses were done using the Kaplan–Meier method and were compared using a log-rank test. The hazard ratio (HR) for specific variables with respect to survival was calculated using Cox proportional hazard regression model. The two-sided

$p < 0.05$ was considered statistically significant. All statistical calculations were performed using SPSS version 23 (Armonk, New York, United States).

Results

Patient Characteristics

A total of 54 consecutive patients, who received low-dose nivolumab from January 1, 2018 to February 14, 2020 were included in this study; 4 patients were not radiologically evaluable. The baseline characteristics of all the patients ($n = 54$) are depicted in ►Table 1.

Table 1 Baseline demographics ($n = 54$)

1. Age – median (range) (y)	50.4 (35–74)
2. Sex – *n* (%)	
Male	46 (85)
Female	8 (15)
3. ECOG-PS – *n* (%)	
< 2	48 (89)
≥ 2	6 (11)
4. Comorbidity – *n* (%)	
Hypertension	12 (22)
Diabetes	6 (11)
Hypothyroidism	3 (5.5)
Bronchiectasis	1 (2)
Cardiac disease	1 (2)
Stroke	1 (2)
None	32 (59.3)
5. Addiction – *n* (%)	
Oral tobacco	31 (57.4)
Smoker	5 (9.3)
Alcohol	4 (7.4)
None	18 (33.3)
6. Sites of disease – *n* (%)	
Urinary bladder	3 (5.6)
Renal	4 (7.4)
Lung Adenocarcinoma Squamous cell carcinoma	9 (16.7) 8 1
Head and neck Oral cavity Oropharynx Larynx Nasopharynx Melanoma	38 (70.4) 28 5 2 2 1
7. Palliative reason	
Initial metastatic	2 (4)
Recurrent/relapsed	52 (96)
8. Number of prior lines of therapy – *n* (%)	
0	2 (3.7)
1	29 (53.7)
≥ 2	23 (42.6)

Abbreviation: ECOG-PS, Eastern Cooperative Oncology Group performance score.

The median age was 50.4 years (range 35–74 years) and male:female ratio was 6:1. Forty-eight (89%) patients had Eastern Cooperative Oncology Group performance score (ECOG-PS) of 0 to 1. The most common comorbidities were hypertension, diabetes, and hypothyroidism seen in 12 (22.2%), 6 (11.1%), and 3 (5.5%) patients, respectively. The majority of the patients (70.4%) were of head and neck cancer and the remaining were of lung (16.7%), renal (7.4%), and urinary bladder (5.6%). Nivolumab was planned as second-line palliative therapy in 29 (53.7%) patients, and as third-line or beyond in 23 (42.6%) patients.

Outcomes

The median follow-up duration was 4.5 months (range 0.5–11.7). The median PFS and OS for the cohort was 2.5 months (95% confidence interval [CI]: 1.8–3.1) and 4.2 months (95% CI: 0.0–9.1) (►Figs. 1 and 2). Partial response and stable disease were achieved in 9 (18 %) and 5 (10 %) patients, respectively (►Table 2). Clinical benefit rate, which included partial and stable disease along with symptomatic improvement in radiologically nonevaluable patients, were seen in 18 (33.3%) patients.

The outcomes were also compared based on radiologic response to the low-dose nivolumab. Six months PFS and OS were 100 versus 8.7% (HR 0.05, 95% CI: 0.01–0.36; $p = 0.003$) and 100 versus 29.7% (HR 0.03, 95% CI: 0.00–0.95; $p = 0.047$), respectively, for responders and nonresponders (►Fig. 3). Median survival was not reached for patients who responded to immunotherapy.

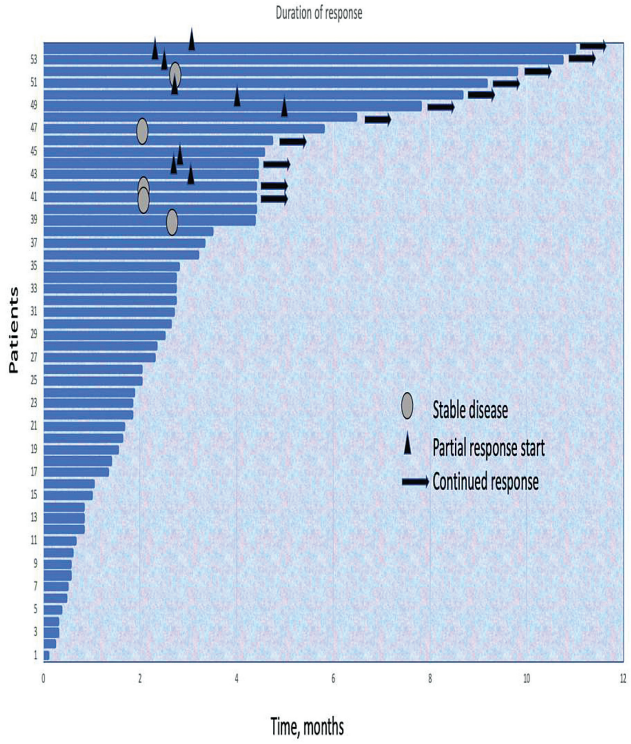

Fig. 1 Duration of response.

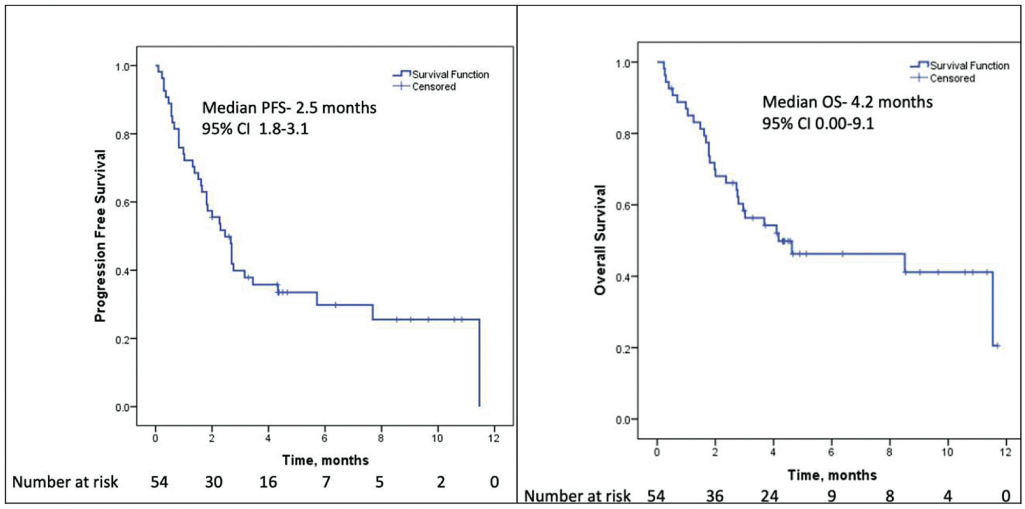

Fig. 2 Progression-free survival and overall survival.

Table 2 Treatment received

Number of cycles of nivolumab	
< 2	13
2–4	25
5–8	10
9–12	3
> 12	3
Best response in radiologically evaluable patients, $n = 50$	
Partial response	9 (18)
Stable disease	5 (10)
Progressive disease or death	36 (72)
Symptomatic benefit ($n = 54$)	
No	36 (66.7)
Yes	18 (33.3)
Antibiotics required during immunotherapy, *n* (%)	5 (9.3)
Site of progression (overlapping), *n* (%)	
Local	26 (72.2)
Distal	
tLung Bone Liver Brain Adrenal Pericardial effusion Nodal	4 (11.1) 4 (11.1) 2 (5.6) 1 (2.7) 1 (2.7) 1 (2.7) 3 (8.3)
Postprogression treatment	
N (%)	10 (18.5)
Chemotherapy Targeted therapy Metronomic	5 2 3
Toxicity - any grade, *n* (%)	25 (46.3)
Transaminitis	5 (9.2)
Pneumonitis	3 (5.6)
Nephritis	3 (5.6)
Fatigue	7 (13.0)
Anorexia	3 (5.6)
Skin rash	3 (5.6)
Hyponatremia	10 (18.5)
Hyperkalemia	3 (5.6)
Hypomagnesemia	3 (5.6)
Hyperuricemia	2 (3.6)
Hypercalcemia	4 (7.4)
Hypothyroidism	2 (3.6)
Toxicity – grade3 or more	
Hyponatremia	6 (11.1)

Note: Numbers in bracket indicate percentage unless otherwise stated.

Seventy-two percent of patients had progressed locally. Post-immunotherapy, only 19% patients were able to receive further treatment. All grade toxicities were present in 46% patients; most common being hyponatremia (18.5%), fatigue (13.0%), and transaminitis (9.2%). There were few grade 3 toxicities (hyponatremia 11%).

Discussion

There is very sparse clinical data available for low-dose immunotherapy, though it is utilized in real-world settings. This study evaluated the safety and efficacy of low-dose nivolumab in the real-world setting for patients with advanced solid malignancies.

Nivolumab is a monoclonal antibody (MoAb) of immunoglobulin G4 (IgG4) subtype that hinders the interaction

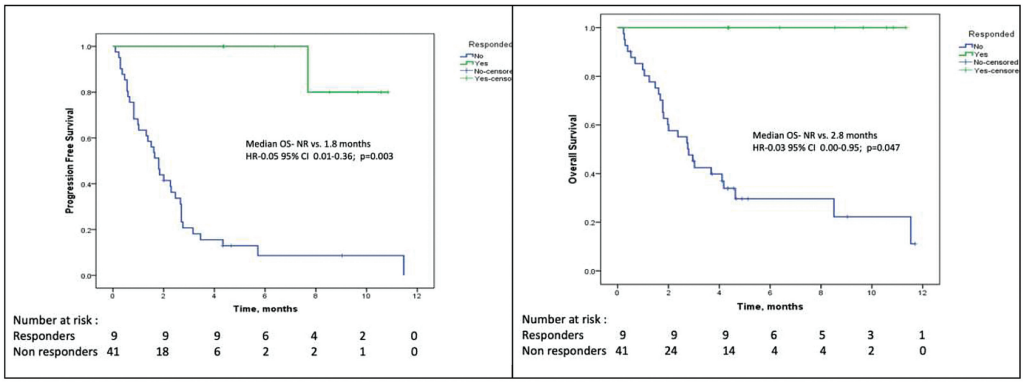

Fig. 3 Progression-free and overall survival in responders and nonresponders.

between the coinhibitory immune receptor PD-1 and its ligands, PD-L1 and PD-L2. IgG4 MoAbs are distinguished by a relatively high molecular mass, causing slow distribution in tissues.[13] The elimination half-life of nivolumab is approximately 27 days[14] and it achieves a steady-state at 12 weeks. Presently, nivolumab is prescribed in varied doses and schedules including weight-based and flat dosing, and at 2 to 4 weekly intervals. Their high affinity to the target results in 70% PD-1 receptors occupancy at 0.04 µg/mL, which is below detectable serum levels of 1.2 µg/mL as observed in vitro studies by enzyme-linked immunosorbent assay.[15] This high affinity is confirmed by dose-ranging phase Ib study, which showed that even at dose of 0.3 mg/kg there is saturation of peripheral PD-1 receptor.[16] The clinical pharmacology review from FDA[17] too observed that the trough concentration is more than 16 µg/mL at 3 mg/kg once every 2 weeks dose. This concentration for receptor binding is more than 160 times of the half-maximal effective concentration. Therefore, no significant exposure efficacy has been seen at doses over 0.1 mg/kg.

The first dose to receive approval from FDA was 3 mg/kg every 2 weeks in 2014 which was established on phase I/II dose finding studies, exhibiting tolerability for the varied range of 0.1 to 10 mg/kg, and illustrating activity at 0.1 mg/kg every 2 weeks and higher dose.[5] Subsequently, in March 2018, a flat dose of nivolumab was approved based on in vivo studies. It was based on equivalence with initial dosing at a median body weight of 80 kg. However, the median body weight differs by the races and the countries. Most of the low and middle-income countries have median body weight of 50 to 60 kg. The process involved population pharmacokinetic data modeling which were derived from roughly 100 clinical trials to imitate concentrations of nivolumab and to compare flat dosing regimens (240 mg once every 2 weeks, 480 mg every 4 weeks) with 3 mg/kg once every 2 weeks dosing.[18,19] Earlier this analysis showed significant but clinically nonrelevant covariate effects, of which body weight and gender were the most crucial.[20] So, the flat dose–response relationship and wide exposure efficacy of nivolumab clearly showed the possibility that a dose as low as 40 mg will have a fair chance of similar effectiveness as compared with standard dose. This is expected to decrease the financial burden without compromising efficacy. The nonlinear relationships between nivolumab dose and clinical outcomes were also substantiated in other trials with various cancers including melanoma, nonsmall cell lung cancer (NSCLC), and renal cell carcinoma.[21]

Low-dose nivolumab was chosen as the preferred option over the other available chemotherapy options based on clinician discretion, as most of the disease sites have very limited treatment chemotherapy options, especially when the patient is ECOG PS 2, or beyond. Besides, the response rates to chemotherapy after first two lines of therapy are extremely low in most of the solid tumors. However, an ideal scenario would have been to do a randomized study to compare the safety and efficacy of low-dose nivolumab with the chemotherapy of physician's choice; however, this is a real-world study with its limitations.

The response rate to standard dose immunotherapy in different cancers in palliative settings poststandard first line varies from 13% in head and neck cancer,[2,3] 17% in NSCLC,[22] 20% in urinary bladder,[23] to 25% in renal cell cancer.[24] Importantly, the responses are maintained for a long duration. We observed a similar trend in our study too. The response rate in previous phase 1 study for low-dose nivolumab was up to 24%.[5] In phase Ib Keynote-012 trial, the response rate was similar (18%).[25] The response rate of 16.7% seems at par with previous studies of standard dose immunotherapy. Patil et al conducted first-ever randomized study and demonstrated that the addition of low-dose nivolumab to metronomic chemotherapy improved OS and is an alternative standard of care for those who cannot access full-dose checkpoint inhibitors.[26]

In this study, the OS was lower than that from the trials.[2,24] In the Checkmate 141 study, in first-line setting for relapse/metastatic head and neck cancer, the response rate was 19.2%; median PFS and OS were 2.3 (1.9–3.3) months and 7.7 (3.1–13.8) months; while the overall response rate (in which 54.5% received two or more lines of therapy) was 13.3%; median PFS was 2.0 months (95% CI, 1.9–2.1) and median OS 7.5 months (95% CI, 5.5–9.1).[2,27] In the present study, we showed similar response rate and PFS but inferior OS. The cause of lesser OS could stem from the fact

that patients present at relatively advanced stage of disease with higher disease burden and limited options of therapy after progression on first two lines of the therapy. Considering the fact that low-dose nivolumab requires lower costs, our finding suggests that this could be a cost-effective option in advanced disease.

Adverse event was seen in 46% of patients with only 11% having grade 3 hyponatremia. The toxicity seems to be similar to that with the conventional doses (59%).[2] It should be noted that hyponatremia was the only grade 3 adverse effect found in this study; however, it is likely related to the disease (70.4% of the patients included in the study had advanced head and neck cancer).

Based on available data and discussion, it seems that lower doses of immunotherapy based on receptor occupancy may be as effective as standard doses and will have marked effect on the cost. The financial burden of treatment with immunotherapy drugs restricts a lot of advanced cancer patients to get standard of care treatment. A study from India has already demonstrated that less than 3% of cancer patients receive immunotherapy.[28] However, the reduced doses are still feasible in a significantly larger number of patients. The lowest possible dose that still demonstrates antineoplastic effect needs to be established.

This study has multiple limitations. First, the retrospective design of the study with its inherent biases and patients of multiple primaries were included. Second, there was selection bias of patients in this data. Third, the sample size is too small to make firm conclusion. Despite these constraints, this clinical study shows the effectiveness of low-dose nivolumab. This concept needs to be investigated in prospective studies.

Conclusion

Low-dose nivolumab has a potential efficacy in the palliative settings. Larger studies are required to establish the efficacy and safety of low-dose nivolumab.

Conflict of Interest

None declared.

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