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Immune checkpoint inhibitors: Real-world experience from India in advanced solid cancers that have progressed on chemotherapy

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Abstract

Context: The immune checkpoint inhibitors (ICIs) nivolumab and pembrolizumab have shown dramatic efficacy with low toxicity in international studies of advanced solid cancers. No published Indian experience with ICIs exist other than isolated case reports. **Aims:** The aim of this study is to evaluate real-world data about the efficacy and toxicity of ICIs in advanced solid cancers among Indian patients who have progressed on one or more prior lines of chemotherapy. **Materials and Methods:** All patients with advanced solid cancers who received ICIs after the failure of chemotherapy at our center were retrospectively assessed. Information about efficacy and toxicity was collected and analyzed. **Results:** The present study included 24 patients who had received ICIs for indications including non-small cell lung, bladder, head and neck, gastrointestinal, and unknown primary cancer. Patients had received a median of two prior lines of chemotherapy (range 1–5). Grade III or higher toxicity was seen in 8% of patients. Clinical benefit at 3 months was realized in 33% of evaluable patients. Twenty-six percentages of evaluable patients achieved a response, including one patient who achieved a complete response that is ongoing at 18 months. Median progression-free survival was 3 months, and median overall survival was 8 months at a median follow-up of 10 months. Among patients who achieved clinical benefit, the majority (84%) have an ongoing response at the time of data cutoff. **Conclusions:** Efficacy and toxicity of ICIs in the Indian population are similar to the experience seen in large international cohorts, and Indian oncologists may feel reassured using these agents in similar settings.

Key words: Bladder cancer, head-and-neck cancer, immunotherapy, lung cancer, metastatic cancer, nivolumab, oral cancer, pembrolizumab

Introduction

Immune checkpoint inhibitors (ICIs) are considered revolutionary agents in the treatment of metastatic solid cancers and have led to transformative developments in this field in the past few years.[1] The discovery of the programmed cell death protein 1 (PD-1) pathway led to the clinical development of PD-1 inhibitors (namely nivolumab and pembrolizumab) which have revealed efficacy in the metastatic setting for some solid cancers in large randomized international phase III clinical trials. The use of these novel agents has been transformative for the treatment of advanced lung cancer,[2-5] urothelial cancer,[6,7] head-and-neck cancer,[8] and gastrointestinal (GI) cancer,[9,10] and is endorsed by major international guidelines issued by professional societies. The generally low toxicity and improved quality of life seen with these drugs (in comparison to chemotherapy) are an added advantage.

The recent availability of these drugs in the Indian market has led to a slow adoption over the past 2 years, with the high cost of these drugs being the main impediment.[11] Nevertheless, this adoption is primarily guided by Western data and there is a dearth of published real-world experience with these drugs in the Indian population to justify their high costs and risk of immune-related adverse effects (IRAEs).[12] The currently published Indian data are restricted to isolated case reports.[13,14] Therefore, we designed a retrospective study looking at all patients who received ICIs at our center in North India over the past 2 years to assess their efficacy and toxicity in our population.

Materials and Methods

Patient selection

Using the hospital information systems, treatment records of all patients with metastatic solid cancers who received PD-1 antibodies (Nivolumab/Opdyta or Pembrolizumab/Keytruda) were retrospectively reviewed. Information was retrieved from medical records, and telephonic follow-up was conducted with families of all the patients concerned to complete missing records. Patients who received <4 weeks of therapy were excluded from the study.

Treatment

ICIs were delivered at our institute by standard procedure as an intravenous infusion. Nivolumab was given at a dose of 3 mg/kg once every 2 weeks by IV infusion. Pembrolizumab was given at a dose of 2 mg/kg every 3 weeks by IV infusion. Therapy was continued until progression or unacceptable toxicity. Dose modifications were permitted for severe toxicity and recorded when done. Response assessment was done clinically after each cycle and radiologically after 2 months of therapy and thereafter every 2-3 months of therapy. RECIST criteria were used to document progression. Patients who progressed on immunotherapy were eligible to receive alternative systemic therapy (chemotherapy and/or targeted therapy) if felt fit for the same by the treating team.

Statistical analysis

IBM SPSS statistics version 20 (IBM corporation, United States of America) was used for statistical analysis. Clinical benefit rate (CBR) was defined as the proportion of patients without clinical or radiological progression at 3 months. Overall survival (OS) was defined as the period from the date of start of immunotherapy to the date of death from any cause. Progression-free survival (PFS) was defined as the time period from the date of start of immunotherapy to the date of radiological/clinical progression of disease or death due to any cause. Kaplan–Meier analysis was performed to evaluate OS and PFS. Categorical variables were compared using Chi-square test or Fisher's exact test when indicated. Predictive

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factors for OS or PFS were analyzed through Cox regression analysis. All analyses were censored at 15 April 2018.

Results

Baseline characteristics

Records of 33 patients with metastatic solid cancers treated at the center were retrieved. From this cohort, nine patients who received <4 weeks of therapy were excluded from the study. The remaining 24 patients constituted the study group. The baseline characteristics of these 24 patients are described in Table 1. The median age was 62 years, with 58% of patients aged >60 years. The majority of patients (79%) were male. The cohort included five patients with head-and-neck cancer, eight patients with non-small cell lung cancer (NSCLC), four patients with bladder cancer, six patients with GI cancer, and one patient with carcinoma of unknown primary site. Thirteen patients (54%) had adenocarcinoma and eight (33%) had squamous cell carcinoma histology, with the remaining three having urothelial carcinoma. Liver, lung, bone, and brain metastases were noted in 21%, 29%, 29%, and 8% of patients, respectively. All patients had received 1–5 prior lines of chemotherapy, with a median of two lines of treatment before immunotherapy.

Treatment and toxicity

All but two patients received nivolumab as immunotherapy, attributed primarily to the delayed approval of pembrolizumab in the country. Grade III or higher toxicity was documented in two patients (8%). One patient developed severe incapacitating fatigue (Grade III) which resolved with dose reduction. Another patient developed severe heart failure with no other apparent cause (Grade V) which resulted in his death after only two cycles of therapy. Therapy was well tolerated in the rest of the cohort with no other treatment interruptions or dose reductions being required.

Clinical benefit and response

A clinical benefit (defined as nonprogression at 3 months of therapy) was realized in 7/21 patients who have completed >3 months of therapy, translating to a CBR of 33%. Among 19 patients evaluable for response, there was one complete remission (5%), four partial remissions (21%), one patient with disease stabilization (5%), and progressive disease in the remaining 13 (68%). The clinical benefit according to the underlying cancer type is described in Table 2. Although patient numbers are small, the CBR was 50% among eight NSCLC patients, 33% among three urothelial cancer patients, and 0% among three GI cancer patients.

Progression-free survival and overall survival

The median follow-up for the entire cohort was 10 months. The median PFS in the overall cohort was 3 months and the median OS was 8 months from the diagnosis [Figure 1 and 2].

Among the seven patients who achieved clinical benefit, the outcomes were significantly improved, with neither median PFS nor OS reached. In fact, at the time of data cutoff, only one of these patients has developed subsequent progression and death, and 84% have maintained a continuous response. The longest duration of response is 18 months, in a patient with NSCLC who had failed two prior lines of chemotherapy but achieved a complete remission with immunotherapy which is still ongoing.

In a multivariate Cox regression analysis, including age >60, gender, histology (adenocarcinoma or squamous), number of prior lines of therapy (single or more), radiation exposure, and sites of metastases, no statistically significant independent risk factors for PFS or OS were realized.

Table 1: Baseline characteristics

Parameter	Value
Age (years), median (range)	62 (40-74)
Male gender, *n* (%)	19 (79)
Underlying malignancy, *n* (%)	
Head and neck	5 (21)
Non-small cell lung	8 (33)
Bladder	4 (17)
Gastrointestinal	6 (25)
Unknown primary	1 (4)
Lung metastases, *n* (%)	7 (29)
Liver metastases, *n* (%)	5 (21)
Brain metastases, *n* (%)	2 (8)
Bone metastases, *n* (%)	7 (29)
Number of prior lines of therapy, *n* (%)	
0	0
1	8 (33)
2	9 (38)
3	5 (21)
4	1 (4)
5	1 (4)
Prior radiation exposure, *n* (%)	14 (58)
Histology, *n* (%)	
Adenocarcinoma	13 (54)
Squamous cell carcinoma	8 (33)
Urothelial cancer	3 (13)

Table 2: Clinical benefit according to the site of origin

Cancer type	Number of evaluable patients	Clinical benefit (%)
Head and neck	4	1 (25)
Non-small cell lung cancer	8	4 (50)
Bladder	3	1 (33)
Gastrointestinal	4	0
Carcinoma of unknown primary site	1	1 (100)

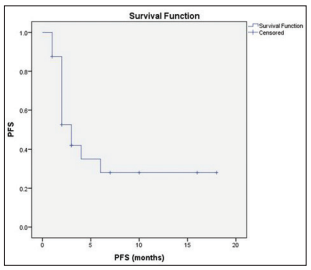

Figure 1: Progression-free survival using Kaplan–Meier analysis

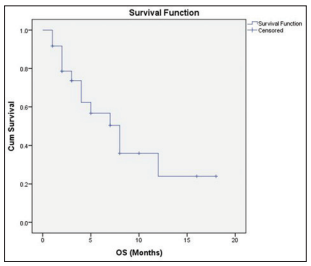

Figure 2: Overall survival using Kaplan–Meier analysis

Discussion

ICIs are generally acknowledged to be a new revolution in cancer therapy. These agents work by inhibiting immune checkpoints that permit an immunosuppressive interaction between the cancer and the adaptive anticancer immune system.[1] This distinct mechanism of action has translated into clinical efficacy; impressive results have been seen in large international trials of metastatic solid tumors, initially in the relapsed setting[2,4-9] and now, increasingly, in the frontline

setting.[3,15] In fact, the impressive results of these agents have led to their recent entry into the adjuvant setting, a trend that was expected to continue.[16] The use of these agents is approved by regulatory agencies and recommended by international guidelines.

Unfortunately, use of these novel agents is associated with significant expense. In fact, a single dose of these drugs may cost more than a complete course of chemotherapy treatment at the present time. The financial limitations of cancer care in the Indian population cannot be overstated.[17] Furthermore, whereas many trials have revealed substantial safety with ICIs, IRAEs are unusual adverse effects that can even be life-threatening in some cases. In this circumstance, publication of real-world Indian data would help our colleagues judge the risk-benefit ratio of these drugs more effectively in our population. This study was conducted to fulfill this deficiency. We here demonstrate our experience with 24 patients who received ICIs for a variety of metastatic solid cancers after the failure of 1–5 lines of frontline chemotherapy.

Therapy was generally well tolerated; only two patients (8%) suffered Grade III or higher toxicity. Various publications emphasize the relatively low risk of serious toxicity with these drugs, with a figure of 7%–20% quoted across various studies.[18] Fatigue is the most common toxicity with ICIs. Although routine cardiac surveillance is not recommended by guidelines at present, we faced one mortality due to heart failure which may have been drug induced. The risk of fulminant ICI-associated myocarditis has recently gained attention among oncologists and is believed to be early toxicity that generally occurs within the first few doses, similar to what was seen in our patient.[19]

The choice of CBR as an endpoint is prompted by the interesting pattern of response seen in many trials of these drugs, where many patients may achieve prolonged disease stabilization instead of responses as seen in conventional chemotherapy. In fact, some patients may respond in the form of a slow progression of disease followed by stabilization.[1,20] The setting in which we used ICIs (metastatic solid tumors after failure of chemotherapy) means that without antitumor activity, disease stability at 3 months is very unlikely. The achievement of a CBR of 33% and an overall response rate of 26% is somewhat similar to what has been seen in many[2,4-7] (but not all)[8] of the large prospective studies conducted in the second-line setting in various cancers, where response rates have been roughly near the 20% of mark in the overall cohorts. Cancer subtype-specific CBR is depicted in Table 2, but this data should be considered of very limited value due to the small number of individual patients in each group.

The median PFS and OS also have some similarity with published prospective experience in large international trials. In unselected cohorts, median PFS has generally been noted to be in the range of 2–4 months and OS in the range of 6–12 months in the relapsed setting.[2,5-8] An interesting phenomenon noted in many immunotherapy trials is the long durations of response realized among treatment responders.[5] Similar findings have been noted in our cohort, whereby most patients who achieved clinical benefit have ongoing responses, with median PFS not reached at the time of data cutoff.

We could not find any clinical parameter that predicted response (or lack thereof) to ICIs in our cohort. Whereas the small sample size of the study may well be the most likely reason, clinical parameters have by and large failed to reveal predictive value in most of the international studies. A large amount of research is being directed toward discovering the true predictive markers for treatment response to ICIs, with stress on molecular parameters such as PD-L1 expression or genetic mutations. This represents an important area of the future study which was not addressed in our study.

The most important limitations of our study are the limited sample size, the heterogeneity of patients regarding underlying cancer and histology, and the use of a retrospective design which introduces significant limitations of selection and recall bias. Prospective validation is required to further strengthen these inferences.

Conclusions

We present the first systematic study looking at real-world experience with ICIs in the Indian population with advanced solid tumors that have progressed on chemotherapy. The efficacy and toxicity seen in our patients largely appear comparable with international experiences, and physicians should feel reassured using these agents in similar settings. With the expanding availability of multiple treatment options in cancer at every stage, predictive markers gain an enhanced importance. We anticipate that the future will see an increasingly personalized, genomic approach to the selection of patients for various treatments. With the pattern of response seen with immunotherapy (deep and prolonged responses seen in a minority of patients) these predictive biomarkers gain especial importance.

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Conflicts of interest

There are no conflicts of interest.

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