Clinical Outcomes of Patients With Metastatic Cancer Receiving Immune Checkpoint Inhibitors in the Inpatient Setting

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Purpose: As indications for immune checkpoint inhibitor (ICI) therapy have increased in recent years, so has the proportion of patients eligible for this type of therapy. However, a lack of data exists about the risks and benefits of ICI therapy in hospitalized patients, who tend to be frailer and sicker than patients enrolled in clinical trials.

Methods: We conducted a retrospective cohort study among hospitalized patients with metastatic solid tumors who received ICI therapy at our institution, a large academic cancer center, over the course of 4 years. We analyzed the characteristics and outcomes of these patients and identified demographic and clinical factors that could be used to predict mortality.

Results: During the 4-year study period, 106 patients were treated with ICI therapy while admitted to the hospital; 66% of them had Eastern Cooperative Oncology Group (ECOG) Performance Status ≥2, which would have prevented them from enrolling in most clinical trials of ICIs. Fifty-two patients died either during admission or within 30 days of discharge; median overall survival was 1.0 month from discharge, and 15% of patients were alive 6 months after discharge. Independent predictors of death following receipt of inpatient ICI included age ≥65 years, having a cancer type other than melanoma, and prior treatment with two or more lines of therapy.

Conclusions: The poor overall outcomes observed in this study may give clinicians pause when considering ICI therapy for hospitalized patients, particularly those with characteristics that are associated with a greater risk of mortality.

Table of Contents

Glossary of Abbreviations

CCI: Charlson Comorbidity Index

ECOG: Eastern Cooperative Oncology Group

EHR: electronic health record

FDA: Food and Drug Administration

HR: hazard ratio

ICI: immune checkpoint inhibitor

irAE: immune-related adverse event

LOS: length of stay

NSCLC: non-small cell lung cancer

OS: overall survival

PS: performance status

Project Description

Scholarly Project Question

Immune checkpoint inhibitors represent an exciting new advance for the treatment of many cancers, but data supporting the effectiveness of these drugs largely comes from clinical trials. Hospitalized patients are generally sicker and more frail than those patients enrolled in trials, and little is known about the risks and benefits of checkpoint inhibitors in a hospitalized population. Nevertheless, these medications are used with regularity in the inpatient setting. The goals of this project were to characterize the patients receiving inpatient checkpoint inhibitor therapy and identify predictors of poor outcomes, helping to guide future decisions about inpatient checkpoint inhibitor use.

Student Contribution

The genesis of this question grew out of the Essentials II class, which I took in October 2018. At that time, I learned about payment structures and also had discussions regarding the ethics of rationing and end of life care. I wanted to apply these topics to a research project within the world of immuno-oncology. At the same time, internal discussions were occurring at Massachusetts General Hospital, where oncologists, pharmacists, and hospital administrators struggled with when, if ever, to offer these expensive and relatively unproven therapies to sick patients who were often near the end of life. Along with my mentor, Dr. Kerry Reynolds, the director of inpatient oncology at MGH, I designed this retrospective study. I executed all of the data collection, the initial statistical analysis, and the drafting and editing of the manuscript. I have presented my work internally at MGH, including at the Cancer Center Clinical Directors meeting and the Pharmacy Therapeutic and Safety Committee, as well as at a large national meeting. The roles of the collaborators are as follows: additional statistical support (AN), initial pharmacy database mining to identify potential cases (CM), help with study design (LP and KR), and abstract/manuscript editing and expert opinion (LZ, AB, RS, TM, IA, DL, JC, EH, DR).

Citation

The manuscript is currently under review in an oncology journal and is not yet published. A version of this project was presented as a poster at the American Society of Clinical Oncology annual meeting in June 2019.

Clinical outcomes of patients with stage IV cancer receiving immune checkpoint inhibitors in the inpatient setting. Sienna Durbin, Leyre Zubiri, Andrzej Niemierko, Laura A Petrillo, Aditya Bardia, Ryan J. Sullivan, Corey McEwan, Therese Marie Mulvey, Ian Matthew Allen, Donald P. Lawrence, Justine Vanessa Cohen, Ephraim P. Hochberg, David P. Ryan, and Kerry Lynn Reynolds. Journal of Clinical Oncology 2019 37:15_suppl, 6634-6634

Introduction

Since the Food and Drug Administration (FDA) approved ipilimumab for the treatment of advanced melanoma in 2011, FDA-approved indications for immune checkpoint inhibitor (ICI) therapy have expanded rapidly in the United States[1]. Consequently, the proportion of patients eligible for ICI therapy has increased substantially, from 26.9% in 2015 to 43.6% in 2018[2]. FDA approvals are based on data from clinical trials that evaluate safety and efficacy in a highly controlled research setting, and these trials typically exclude patients with poor performance status (PS) and significant comorbidities[3-7]. However, the rapid adoption of ICI into clinical practice includes expansion of its use to inpatient wards, where patients often have poor functional status and significant comorbidities.

Prior studies have shown that administering cytotoxic chemotherapy during inpatient admission leads to poor outcomes, including high mortality and aggressive end-of-life care; it is unknown whether this is also true for administering ICI therapy[8]. This absence of data makes it difficult for physicians to identify which inpatients are likely to benefit from initiating ICI therapy, which is particularly challenging as many admitted patients do not have a prognosis that allows physicians to try multiple lines of therapy. This, along with the high cost of ICI therapy and the fact that more and more patients will become eligible for ICI therapy in the future, makes the need for real-world clinical data on ICI use in hospitalized patients a pressing one.

To aid future decisions regarding ICI use in the inpatient setting, we conducted a retrospective cohort study among hospitalized patients with metastatic solid tumors who received ICI therapy at our institution, a large academic cancer center, over the course of 4 years. The objectives of this study were to characterize the patients receiving inpatient ICI therapy and to identify predictors of poor survival.

Methods

Study design. We conducted a retrospective cohort study of patients with metastatic solid tumors who received ICI therapy while admitted to an inpatient ward between January 1, 2015 and December 31, 2018 at a large referral hospital associated with an academic cancer center. Patients who were treated with ICI therapy (including anti-PD-1, anti-PD-L1, and anti-CTLA-4 as monotherapy or in combination) were identified using pharmacy records. The study was

conducted at Massachusetts General Hospital (MGH), Boston, MA, USA, and approved by the Partners Healthcare Institutional Review Board.

Inclusion criteria. Our analysis included patients that received their first dose of a new line of ICI during admission, as well as those who continued ICI during admission after beginning therapy within 30 days prior to admission. We included patients who received single-agent or combination ICI therapy, as well as those treated with chemotherapy-ICI combination therapy.

Exclusion criteria. In order to limit the variability in patient population, those with hematologic or primary neurologic malignancies were excluded, as were patients receiving ICI as part of a clinical trial.

Data extraction. We used patients' electronic health records (EHRs) to extract data on patient characteristics, including age, sex, tumor type, type of ICI administered, length of stay (LOS), ICI administration (e.g., whether treatment continued following discharge), post-discharge oncology clinic visits, and readmissions to the same healthcare system within 30 days. Eastern Cooperative Oncology Group (ECOG) PS was determined by the treating oncologist at the time of admission or at the time of new diagnosis, where appropriate. We determined Charlson Comorbidity Index (CCI) scores based on comorbidities documented at the time of admission[9]. We defined the reason for admission based on the clinical rationale documented in the admission note and discharge summary. Number of prior lines of therapy was determined based on admission documentation and outpatient oncology progress notes. Time of diagnosis of metastatic disease was calculated based on EHR documentation and pathology reports. We captured discharge location (home, rehabilitation facility, home with hospice services, or hospice facility) from discharge summary documentation. FDA approval status of the ICI administered was determined by cross-referencing the date of ICI approval for specific tumor types with the date of ICI administration. We determined whether patients experienced immune-related adverse events (irAEs) using oncology clinic progress notes and discharge summaries that documented clinician diagnoses and the decision to monitor or treat; assessment of irAEs was censored as of June 30, 2019. We extracted dates of death from EHRs; date of last contact with the healthcare system was substituted where date of death was not documented. Follow-up was censored at June 30, 2019.

Statistical Analysis. A multivariable Cox proportional hazards regression model was used to identify predictors of death. All independent variables analyzed were categorical, with cutoff

values determined either according to a pre-existing rationale or to achieve roughly equal sample sizes in each category. Age categories were <65 years and ≥65 years; PS categories were ECOG 0–1, ECOG 2, and ECOG 3–4; CCI categories were 6–8 and ≥9; tumor type categories were melanoma, non-small cell lung cancer (NSCLC), or "other"; prior treatment line categories were 0, 1, or ≥2; FDA approval categories were yes or no. Categories for time from diagnosis to administration of inpatient ICI therapy were 0–37 days, 38–116 days, 117–468 days, or 469–2430 days, determined by quartiles. P-values of <0.05 were considered statistically significant.

We also calculated the time from ICI administration to death from any cause to determine median overall survival (OS). The survival curve was estimated using the Kaplan-Meier method.

Statistical analyses were carried out using R and Stata statistical softwares.

Results

During the 48-month study period, 106 patients were treated with ICI therapy while admitted to the hospital. The characteristics of these patients are shown in Table 1. The median patient age was 59.5 years, and 57.5% of patients were male. Melanoma was the most common indication for ICI (32.1%), followed by NSCLC (19.8%). PS at the time of admission ranged from ECOG 0 to ECOG 4, with ECOG 2 being the most common, and CCI scores ranged from 6 to 15, with scores of 6–8 being the most common. Thirty-five percent of patients had received no prior lines of therapy; thirty percent had received one prior line of therapy for their cancer. Time from diagnosis of metastatic disease to administration of inpatient ICI ranged from 2 days to 6.7 years, with a median time of 116 days. Over half of all patients were admitted for complications of tumor progression (53.8%) and 15.1% of patients were admitted because they were newly diagnosed with cancer. The remaining 31.1% were admitted for a range of indications, including infection and scheduled surgery, which were not thought by the primary team to be directly related to progression of malignancy. The most frequent ICI used was pembrolizumab, either as monotherapy (35.8%) or in combination with chemotherapy (6.6%). The next most frequent was nivolumab (33%), followed by combination ipilimumab/nivolumab (12.3%). The majority of patients (62.5%) had a tumor type and indication for which treatment with ICI therapy was approved for use by FDA at the time of drug administration; the other patients were treated off-label or through a compassionate use program.

The median LOS for the 106 patients treated with ICI therapy was 12.5 days (Figure 1). Nearly a quarter of patients (23.6%) died during the admission; 47.1% were discharged to home, 21.7% to rehabilitation facilities, and 7.5% to hospice facilities or home with hospice services. Of those discharged from the hospital, 55.6% were readmitted within 30 days. The majority (71.6%) of discharged patients had a follow-up visit with an outpatient oncologist, and 49.4% of patients continued to receive ICI therapy after discharge from the hospital. Of those patients who continued to receive ICI, 47.5% received more than 3 doses following discharge.

Fifteen patients (14%) had an irAE documented in the EHR, most commonly colitis (4 patients, 3.8%) and pneumonitis (3 patients, 2.8%). Other documented irAEs included seizure (2 patients, 1.9%), hepatitis, hypothyroidism, diabetes, myocarditis, mucositis, and rash (1 patient each, or 0.9%). Most of these toxicities did not occur during admission but were identified later in follow up; only two irAEs (rash and mucositis) occurred in the same admission during which ICI therapy was administered. Median time from receipt of inpatient ICI to first documentation of an irAE was 63 days (range 6 to 163 days).

To identify predictors of death following inpatient ICI and mitigate potential confounding effects, we performed a Cox multivariable regression analysis incorporating age, PS, CCI score, tumor type, prior lines of therapy, FDA approval status, and time from diagnosis of metastatic disease to receipt of ICI as an inpatient (Table 2). Tumor type was a significant predictor of death following inpatient ICI, with NSCLC (HR 2.10; $P = 0.036$) and "other" solid tumors (i.e., those "other" than melanoma or NSCLC; HR 1.91; $P = 0.036$) associated with shorter OS than melanoma. Number of prior lines of therapy also predicted mortality, with two or more prior lines associated with shorter OS relative to first-line treatment (HR 2.32; $P = 0.049$), as did older age (≥65 years; HR 2.00, $P = 0.048$). CCI score, time from diagnosis of stage IV cancer to receipt of inpatient ICI, and the presence of an FDA-approved indication for the use of ICI were not significantly predictive of OS. Poor performance status (HR 1.69 (0.97 - 2.94) had worse survival, but this finding did not meet statistical significance ($P = 0.063$).

Fifty-two patients (49%) treated with ICI died during admission or within 30 days of discharge, with a median OS of 1.0 months from time of discharge. The proportion of patients alive at 6 months after discharge was 15% (95% CI 9.6–23.7; Supplemental Figure 1). Sixteen patients (15%) were alive at 6 months following discharge; median age was 57.0 years (range 46 to 72) and 81% were male. Sixty-two percent of patients had melanoma, 12.5% NSCLC, 12.5%

gastrointestinal malignancies, 6.25% squamous cell carcinoma of the head and neck, and 6.25% squamous cell carcinoma of the skin. Half of patients (50%) had PS 0-1, 31.3% PS 2, and 19.7% PS 3. No patients had PS 4. In this group, 50% of patients had an irAE documented in the EHR.

Discussion

In this four-year, retrospective study at a single institution, we found that patients who received ICI were more frail and had a higher burden of comorbidity than the participants typically included in clinical trials, and their outcomes after ICI therapy were generally poor. However, a subset of patients (15%) were alive at six months. Our results add real world evidence that describes an understudied population and may be useful to other institutions in deliberating the value of inpatient ICI administration.

Using multivariable analysis, we identified several significant predictors of mortality. Type of cancer was a particularly strong predictor; older age and prior treatment with multiple lines of therapy were also predictive of shorter overall survival following discharge. Our findings suggest that, despite promising clinical trial data for the use of ICI in the treatment of non-melanoma solid tumors, inpatient administration may not be appropriate[4-7]. Inpatient ICI may also be inappropriate in patients who have received multiple lines of therapy prior to admission. Additionally, we note that performance status may be a useful predictor, although it did not reach significance in this dataset, likely due to the small sample size of our dataset and insufficient power to detect a significant difference. The value of performance status in predicting mortality following ICI administration is supported by data from clinical trials of pembrolizumab, which show shorter OS in patients with NSCLC who have PS 2 rather than PS 0–1[10,11]. Real world analysis of patients who received ICI close to end of life has also identified PS 3-4 as a poor prognostic factor[12].

Although the majority of patients died during hospitalization or within 30 days of discharge, a subset of patients was alive at 6 months. Over 50% of these patients had melanoma and half had PS 0-1 on admission, suggesting that patients with good performance status and a more favorable tumor type may be more likely to derive a sustained benefit from inpatient ICI. However, this group was heterogenous, with multiple tumor types represented, indicating that more work must be done to identify correlates of response to ICI to improve prediction of the patients most likely to benefit.

IrAEs are common complications of ICI therapy that, in some cases, can lead to severe morbidity and even death. One might expect irAEs to be more common among the vulnerable patients that we studied. However, the percentage of patients (14%) who experienced irAEs in our sample is no higher than rates seen in the clinical trial population, which have been found to be as high as 66.0% in meta-analysis of trials evaluating PD-1 and PD-L1 inhibitors[13]. Of note, patients in our cohort did experience serious irAEs, including seizure and myocarditis. Myocarditis, especially, can be life-threatening, with fatalities occurring in 50% of cases[14]. Hospitalized patients may have less reserve to tolerate severe toxicity. Additionally, it is possible that the relatively low incidence of irAEs reflects a failure to detect events, rather than a lack of susceptibility in this population. The median time to irAE diagnosis was two months; at this time point, only 32% of patients remained alive. Importantly, the rate of irAEs was substantially higher in the subset of patients that lived six months or longer following discharge, suggesting that the incidence of toxicity in inpatients receiving ICI may approach rates seen in the clinical trial population when patients live long enough for adverse events to occur. This finding is supported by prior work demonstrating that median time to irAE onset ranges from 5 weeks to 15 weeks following anti-PD-1 therapy[15].

This study has several important limitations. First, our findings represent the experience of one institution, and replication is warranted. Second, the utility of our finding that a non-lung/non-melanoma cancer type predicts significantly shorter OS than melanoma is limited by the fact that this "other" category represents a very heterogeneous group of tumors, including head and neck, genitourinary, and non-melanoma skin cancers, among others. Further investigating outcomes for these individual tumor types would be helpful. Third, our analysis of irAEs was limited, as it depended on chart review and provider documentation. Events were not verified using biopsy or laboratory data, so it is possible that some of the irAEs recorded were not, in fact, irAEs, especially given that previous work has demonstrated the limitations of irAE diagnosis and assessment[16]. However, given the relatively low rate of irAEs reported here, the likelihood that false positives inflated the results is low. Finally, this was a retrospective study that lacked a control group; therefore, it is not clear what outcomes these patients would have experienced had they not received ICI therapy.

In conclusion, these results may provide guidance to clinicians deciding whether to administer ICI therapy to hospitalized patients, and help institutions establish guidelines for the

use of inpatient ICI therapy. To the best of our knowledge, this is the only work to date examining outcomes associated with ICI therapy in this important and vulnerable population. We believe the poor overall outcomes observed in this study may give clinicians pause when considering ICI therapy for inpatients, particularly those ≥65 years of age, with poor PS, or with a tumor type other than melanoma. We note that despite the high rate of death following discharge in this study, only 7.5% of patients were discharged with hospice services, either in the home or at a facility. Many patients were probably ineligible for hospice because they were still receiving therapy, but they might have opted for hospice over cancer treatment-focused end-of-life care if they knew of the patterns we observed in this study.

The presence of a small subset of long-term survivors suggests that there are situations in which it may be appropriate to offer inpatient ICI. More work is needed to better characterize this group and understand which patients are more likely to derive benefit from inpatient therapy. Studies focused on specific tumor types, such as melanoma and NSCLC, may help to identify additional prognostic factors specific to these populations. Additionally, future research that incorporates patient-reported outcomes would better characterize the impact of inpatient ICI from the lens of the patient.

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Table 1. Characteristics of patients receiving immune checkpoint inhibitor (ICI) therapy while admitted to the hospital

Characteristics	n	%
Age (years)		
Median	59.5	
Range	26, 85	
Sex		
Male	61	57.5
Female	45	42.5
Tumor type		
Melanoma	34	32.1
NSCLC	21	19.8
Head and neck	17	16.0
Gastrointestinal	14	13.2
Genitourinary	7	6.6
Small cell lung cancer	5	4.7
Gynecologic	4	3.8
Skin (non-melanoma)	4	3.8
Performance status (ECOG)		
0	8	7.5

1	28	26.4
2	38	35.8
3	30	28.3
4	2	1.9
Comorbidities (CCI)		
6–8	66	62.3
≥9	40	37.7
Prior lines of therapy		
0	38	35.8
1	32	30.2
2	18	17.0
3	10	9.4
≥4	8	7.5
Time from diagnosis of metastatic disease to inpatient ICI initiation (days)		
Median	116	
Range	2, 2430	
Reason for admission		
New diagnosis of cancer	16	15.1
Disease progression	57	53.8
Other[a]	33	31.1
Type of ICI administered		
Pembrolizumab	38	35.8
Nivolumab	35	33.0
Ipilimumab/nivolumab	13	12.3
Pembrolizumab/chemotherapy	7	6.6
Atezolizumab	5	4.7
Ipilimumab	5	4.7
Atezolizumab/chemotherapy	3	2.8

FDA-approved indication?		
Yes	66	62.3
No	40	37.7

Abbreviations: NSCLC, Non-small cell lung cancer; CCI, Charlson Comorbidity Index score; ECOG, Eastern Cooperative Oncology Group Performance Status

[a]Other causes (n=1 unless otherwise indicated) include anxiety, bowel perforation, chemotherapy-induced heart failure, new diagnosis of second malignancy, failure to thrive, gastrointestinal bleeding (n=2), hemoptysis, infection (n=13), oropharyngeal bleeding (n=2), pain (n=2), pulmonary embolism, renal failure, scheduled surgery (n=4), stroke, and vasovagal syncope.

Figure 1. Flow chart of outcomes for patients treated with immune checkpoint inhibitor (ICI) therapy during admission to the hospital.

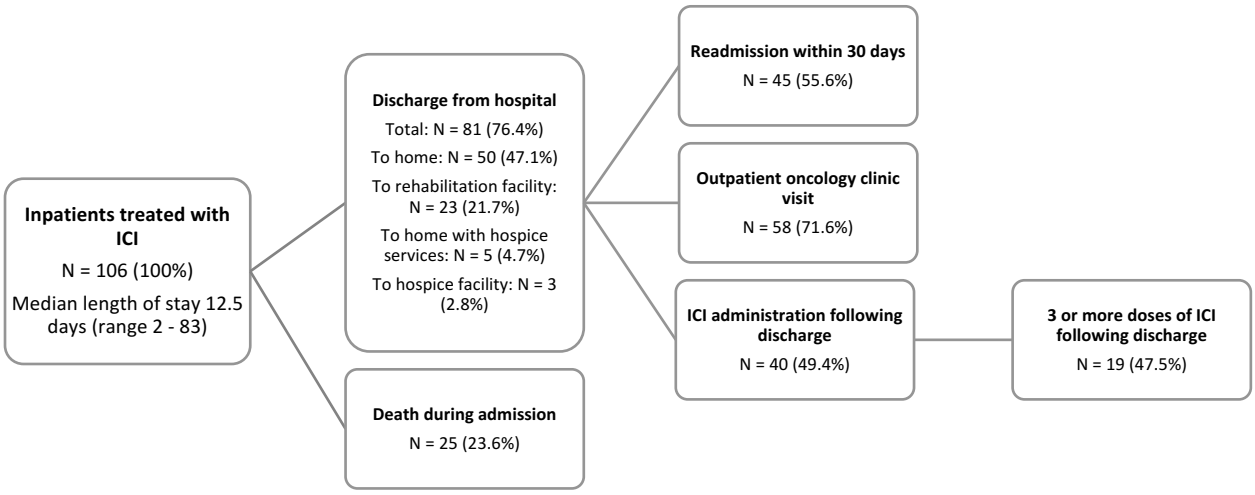

Figure 2. Analysis of which demographic and clinical factors independently predict death for patients treated with immune checkpoint inhibitor therapy during admission to the hospital. Hazard ratios and p-values were calculated using a Cox multivariable regression model. "Time from diagnosis" represents the time from diagnosis of metastatic disease to administration of inpatient ICI therapy. Abbreviations: CI, confidence interval; NSCLC, Non-small cell lung cancer; CCI, Charlson Comorbidity Index score; ECOG, Eastern Cooperative Oncology Group Performance Status score.

Characteristic		**Hazard Ratio (95% CI)**	***P* value**
Age	18-64 years	1 (reference)	
	65+ years	2.00 (1.00 - 3.94)	0.048
Performance Status	ECOG 0-1	1 (reference)	
	ECOG 2	1.12 (0.66 - 1.90)	0.66
	ECOG 3-4	1.69 (0.97 - 2.94)	0.063
CCI Score	6-8	1 (reference)	
	9+	0.70 (0.37 - 1.32)	0.27
Tumor Type	Melanoma	1 (reference)	
	NSCLC	2.10 (1.05 - 4.23)	0.036
	Other Solid Tumor	1.91 (1.04 - 3.50)	0.036
Prior Treatment Lines	0	1 (reference)	
	1	1.03 (0.53 - 2.00)	0.93
	2+	2.32 (1.00 - 5.37)	0.049
FDA Approval	No	1 (reference)	
	Yes	0.86 (0.53 - 1.40)	0.56
Time from Diagnosis	0-37 days	1 (reference)	
	38-116 days	1.04 (0.54 - 2.00)	0.9
	117-468 days	1.23 (0.57 - 2.65)	0.6

	469+ days	0.47 (0.19 - 1.21)	0.12

Supplemental Figure 1 (online). Overall survival in all patients treated with immune checkpoint inhibitor therapy during admission to the hospital. Shown is a Kaplan-Meier estimate of overall survival, with estimated 95% confidence interval. Time 0 represents date of discharge. At 6 months post-discharge, only 16 patients remained alive.