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Brief Communications

Risk of COVID-19 in Patients with Cancer Receiving Immune Checkpoint Inhibitors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Objective. The aim of this study was to determine the rate of coronavirus disease-19 (COVID-19) among patients with cancer treated with immune checkpoint inhibitors (ICIs).

Materials and Methods. This was a retrospective study of 1,545 patients with cancer treated with ICIs between July 1, 2019, and February 29, 2020, and 20,418 age-, sex-, and cancer category-matched controls in a large referral hospital system. Confirmed COVID-19 case and mortality data were obtained with Massachusetts Department of Public Health from March 1 through June 19, 2020.

Results. The mean age was 66.6 years, and 41.9% were female. There were 22 (1.4%) and 213 (1.0%) COVID-19 cases in the ICI and control groups, respectively. When adjusting for demographics, medical comorbidities, and local infection rates, ICIs did not increase COVID-19 susceptibility.

Conclusion. ICIs did not increase the rate of COVID-19. This information may assist patients and their oncologists in decision-making surrounding cancer treatment during this pandemic. ***The Oncologist*** 2021;26:e898–e901

Introduction

The ongoing coronavirus disease-19 (COVID-19) pandemic has resulted in more than 117 million cases and 2.6 million deaths. Immunomodulation by immune checkpoint inhibitors (ICIs), which are used to treat advanced cancers, has an uncertain effect on COVID-19 susceptibility, as it can contribute to both the clearance of SAR-CoV-2 and to the immune overactivation associated with severe COVID-19 [1]. Reported outcomes in these patients are conflicting [2–4]. We compared infection risk between cancer patients with and without history of ICI treatment.

Materials and Methods

Study Participants

Patients treated with ICIs between July 1, 2019, and February 29, 2020, were identified in the Mass General Brigham (MGB) network using Enterprise Data Warehouse. MGB Research Patient Data Registry (RPDR) was used to select controls, matched on age, sex, race, and ethnicity. The 2010 US census was used to determine median income by zip code. COVID-19 status and subsequent all-cause mortality were obtained from the Massachusetts Department of Public Health as of June 19, 2020, matched by patient birth date, last name, and first four letters of the first name. Local infection rate by zip code through June 19, 2020, were obtained from the Massachusetts COVID-19 Dashboard.

To isolate the immunomodulatory effect to the ICI therapy, patients with prescriptions for other immunomodulatory medications were excluded from both groups (supplemental online Table 1). We also excluded patients with incomplete demographic or medical information and those reported as deceased as of February 29, 2020. Finally, we excluded patients residing in zip codes outside of Massachusetts and without available local infection rates. Patients in both groups included in the final analysis were matched using exact matching by age, sex, race and ethnicity, and cancer category (hematologic or solid organ). The study flow diagram is shown in supplemental online Figure 1.

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Table 1. Baseline characteristics of patients with cancer treated with immune checkpoint inhibitors and matched controls

Characteristics	ICI group, *n* = 1,545	Control group, *n* = 20,418	*p* value
Sex: female, *n* (%)	648 (41.9)	8,564 (41.9)	>.999
Age, years			>.999
Mean (SD)	66.6 (12.0)	66.6 (12.0)	
18–44, *n* (%)	952 (4.7)	72 (4.7)	
45–64, *n* (%)	6,965 (34.1)	527 (34.1)	
65–74, *n* (%)	7,480 (36.6)	566 (36.6)	
≥75, *n* (%)	5,022 (24.6)	380 (24.6)	
Race,[b] *n* (%)			>.999
White, non-Hispanic	1,447 (93.7)	19,123 (93.7)	
Asian, non-Hispanic	33 (2.1)	436 (2.1)	
Black, non-Hispanic	32 (2.1)	423 (2.1)	
Other, non-Hispanic	12 (0.8)	159 (0.8)	
Hispanic	1 (0.1)	13 (0.1)	
Unknown	20 (1.3)	264 (1.3)	
CCI grade, *n* (%)			.13
Mild (1–2)	52 (3.4)	834 (4.1)	
Moderate (3–4)	357 (23.1)	5,017 (24.6)	
Severe (≥5)	1,136 (73.5)	14,567 (71.3)	
Cancer type, *n* (%)			
Hematologic cancer	111 (7.2)	1,467 (7.2)	>.999
Solid organ cancer	1,485 (96.1)	19625 (96.1)	>.999
Comorbidities, *n* (%)			
Congestive heart failure	165 (10.7)	2,371 (11.6)	.27
Hypertension	822 (53.2)	9,452 (46.3)	**<.001**
Diabetes mellitus	254 (16.4)	4,204 (20.6)	**<.001**
Chronic obstructive pulmonary disease and bronchiectasis	373 (24.1)	4,477 (21.9)	**.04**
Other chronic pulmonary disease	233 (15.1)	3,766 (18.4)	**<.001**
Renal disease	241 (15.6)	3,290 (16.1)	.59
Liver disease	535 (34.6)	6,452 (31.6)	**.01**
Rheumatic disease	52 (3.4)	926 (4.5)	**<.001**
Inflammatory bowel disease	29 (1.9)	720 (3.5)	**.03**
Median income in $1,000s			**.002**
Missing, *n*	12	144	
Mean (SD)	79.6 (26.8)	81.9 (28.6)	
COVID-19 town or county positivity rate per 100, mean (SD)	1.37 (0.89)	1.38 (0.91)	.68
COVID-19 positive, *n* (%)	22 (1.4)	213 (1.0)	.16
Died, *n* (% of COVID-19 positive)	9 (40.9)	61 (28.6)	.23

[a]As recorded in the electronic medical record.
Abbreviations: CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease-19.

Study Outcomes

The primary outcome was rate of SARS-CoV-2 infection. Secondary outcome was subsequent all-cause mortality among patients with confirmed COVID-19.

Statistical Analysis

Ages were grouped as 18–44, 45–64, 65–74, and ≥75 years. Age-adjusted Charlson Comorbidity Index (CCI) scores were coded as mild (1–2), moderate (3–4), and severe (≥5). Hematologic and solid organ cancers were identified by ICD-9 and ICD-10 codes (supplemental online Table 2). SARS-CoV-2 infection was confirmed by (a) a positive polymerase chain reaction test or (b) a positive serology test and symptoms or known exposure. To compare differences between groups, Fisher's exact and Pearson's chi-square tests were used for categorical variables and two-tailed *t* test was applied for continuous variables. A multivariable

Table 2. Risk of SARS-CoV-2 infection and subsequent all-cause mortality characteristics of patients with cancer treated with ICIs, and matched controls

	OR	95% CI	*p* value
Infection[a]			
History of ICI treatment	1.38	0.89–2.13	.15
Mortality[b]			
History of ICI treatment	1.60	0.78–3.29	.71

[a]Multivariable logistic regression adjusting for age, sex, race and ethnicity, age-adjusted CCI grade, median income, and local infection rate (also presented in suppelemtal online Table 4)
[b]Poisson logistic regression adjusting for sex, age-adjusted CCI grade, median income, and local infection rate (also presented in supplemental online Table 5)
Abbreviations: CI, confidence interval; ICI, immune checkpoint inhibitor; OR, odds ratio.

logistic regression was used to calculate the odds ratio (OR) for COVID-19 diagnosis, after adjusting for age, sex, race, cancer category, CCI severity grade, median income, and local infection rate. A multivariable Poisson regression was used to compare subsequent all-cause mortality among patients with confirmed COVID-19. All analyses were conducted in R version 3.5.3.

Results

A total of 1,545 ICI and 20,418 matched control patients were included in the analyses (Table 1). Mean age was 66.6 years (SD, 12.0), and the majority (93.7%) of patients were White. There were no differences in the age-adjusted CCI severity grades between the two groups (p = .13). In the ICI cohort, 49.1% of patients were treated with pembrolizumab monotherapy (supplemental onine **Table 3**).

Risk of Infection

Twenty-two patients (1.4%) were prescribed ICIs, and 213 (1.0%) control patients were confirmed as COVID-19 positive (p = 0.16). There were no significant differences in infection risk between ICI recipients and matched controls in multivariable modeling (OR, 1.38; 95% CI, 0.89–2.13; p = .15; Table 2). Female sex (OR, 1.74; 95% CI, 1.34–2.25; p < .001), increasing comorbidity burden (OR 9.77 for age-adjusted CCI, ≥5; 95% CI, 1.47–1.71; p = .02) and increasing local infection rate (OR, 1.59; 95% CI, 1.47–1.71; p < .001) were associated with increased infection susceptibility (supplemental online Table 4). Treatment with combination therapy did not increase the risk of infection (supplemental online Table 5).

Risk of mortality

There were 9 (40.9% mortality rate) and 61 (28.6% mortality rate) deaths in the ICI and control groups, respectively (p = .23). ICI treatment did not increase the odds of death (OR, 1.60; 95% CI, 0.78–3.29; p = .71), after covariate adjustment (Table 2). Female sex (OR, 0.47; 95% CI, 0.29–0.78; p < .01) and increasing median income (OR, 0.86; 95% CI, 0.77–0.97; p = .01) decreased mortality risk (supplemental online Table 6). Seven patients (35%) treated with monotherapy and both patients treated with combination therapy died following COVID-19 (p = .15).

Discussion

The overall incidence of COVID-19 was not significantly different between the ICI and control populations, which remained true after adjusting for covariates. We observed that female sex was associated with lower risk of infection. The protective effect of female sex on mortality is well established and was also observed in our study [4–7]. It is possible that female patients might not have presented or met the criteria for testing in the early stages of the pandemic and are underrepresented in prior reports. These studies also did not control for local infection rates, which predicted infection in our study. Increasing comorbidity burden also increased the odds of COVID-19 diagnosis. These patients may be more susceptible to infection or more frequent interaction with the health care system resulting in more frequent testing [1, 4, 6, 7].

Although a higher percentage of ICI patients with confirmed COVID-19 died compared with the control group, these differences in mortality were not statistically significant even after adjusting for covariates, consistent with two prior reports [2,3]. However, Rogiers et al. identified combination therapy as risk factor for hospitalization [3]. Both patients treated with combination therapy died, which may suggest that monotherapy should be used in patients at high risk of COVID-19 mortality when clinically reasonable. Finally, patients living in zip codes with higher median incomes were less likely to die, highlighting the contribution of social determinants of health to outcome disparities during this pandemic [8].

Our study cohort is from a single health care system in Massachusetts, which limits its generalizability. We also did not control for history of smoking or treatment with other anticancer therapies, which may have affected our results [4, 9]. Finally, it is possible that some patients completed their last cycle of ICI therapy before the beginning of the pandemic. However, a pharmacokinetics study of nivolumab showed PD-1 receptor occupancy 1 year following last administration of the drug [10]. Additionally, the prevalence of delayed immune related adverse events in patients treated with a variety of ICIs supports their longitudinal immunologic effect.

Conclusion

ICI treatment did not increase the risk of COVID-19 among patients with cancer. These findings may assist patients and their oncologists making decisions surrounding therapy initiation or continuation during this protracted pandemic.

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Disclosures

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