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Immuno-Oncology

Safety of Immune Checkpoint Inhibitors in Patients with Cancer and Hepatitis C Virus Infection

Akram Alkrekshi, Ila Tamaskar

The MetroHealth System Campus of Case Western Reserve University, Cleveland, Ohio, USA

Key Words. Immune checkpoint inhibitor • Hepatitis C • Immune-related adverse events • Immunotherapy • Retrospective study

Abstract

Background. The safety of immune checkpoint inhibitors (ICIs) in patients with hepatitis C virus (HCV) infection has not been studied in many cancers, as these patients were excluded from most ICI trials. This poses a degree of uncertainty when a patient with HCV is being considered for ICIs in the absence of data to inform potential adverse events (AEs).

Materials and Methods. This was a single-institution retrospective chart review of patients with active or resolved HCV who were treated with ICIs for cancer of any type and stage from January 2012 to December 2019, with emphasis on AE rates.

Results. We identified 40 patients, 30 men and 10 women. Median age was 64 years. Cancer types were non-small cell lung cancer (18; 45%), hepatocellular carcinoma (12; 30%), head and neck cancer (4; 10%), small cell lung cancer (3; 7.5%), renal cell carcinoma (1; 2.5%), colon cancer (1; 2.5%), and melanoma (12.5%). Hepatitis C was untreated in 17 patients (42.5%), treated in 14 (35%), and spontaneously resolved in 9 (22.5%). AEs observed were grade 3 pneumonitis in one patient (2.5%) on pembrolizumab; grade 3 colitis in one patient (2.5%) on nivolumab; hepatotoxicity in two patients (5%) on nivolumab: one patient with grade 1 and the other with grade 2; grade 1–2 fatigue in three patients (7.5%); and hypothyroidism in one patient (2.5%).

Conclusion. Adverse events rates in patients with untreated and resolved HCV treated with ICI for a variety of cancers were comparable with AEs rates reported in clinical trials for patients without HCV. ***The Oncologist*** 2021;26:e827–e830

Implications for Practice: The safety of immune checkpoint inhibitors (ICIs) in patients with cancer with hepatitis C virus (HCV) infection is a major concern because of the lack of prospective safety data for most cancers. HCV is prevalent worldwide, and the occurrence of cancer where ICI is indicated is not uncommon. This study was a retrospective review of all patients with HCV who received ICI for a variety of cancers in the authors' institution over 8 years, and the results are presented in this article. The results may help inform clinical decisions and the design of future clinical trials.

Introduction

Immune checkpoint inhibitors (ICIs), namely programmed death receptor-1 (PD-1) and programmed death receptor-1 ligand (PD-1L) inhibitors and cytotoxic T-lymphocytic antigen 4 (CTLA-4), have changed the cancer therapy paradigm and are approved for various malignancies: melanoma, lung cancer, hepatocellular carcinoma, and many others (Table 1). CTLA-4 and PD-1L are intrinsic downregulators of immunity that dampen the immune regulatory response. Cancer cells hijack this system to evade the immune system. ICIs, by blocking these cell surface proteins, enhance the antitumor immune response. In hepatitis C virus (HCV) infection, the expression of PD-1/PD-1L contributes to the persistence of infection [1]. Therefore, to avoid unforeseen adverse events (AEs; e.g., viral reactivation), patients with HCV infections were excluded from most clinical trials evaluating ICI even though HCV is a major health care problem, with a prevalence of 0.5%–2.3% worldwide [2]. Absence of ICI safety data in patients with cancer with HCV makes it challenging to adequately assess the risk-benefit of ICI and to advise the patient on the likelihood of AEs to assist them in making an informed decision. This may result in ICIs being denied or delayed pending treatment of the underlying

Correspondence: Akram Alkrekshi, M.D., The MetroHealth System Campus of Case Western Reserve University, 2500 MetroHealth Drive, Cleveland, Ohio 44109, USA. Telephone: 216-778 -7800; e-mail: aalkrekshi@metrohealth.org Received April 12, 2020; accepted for publication February 8, 2021; published Online First on March 20, 2021. http://dx.doi.org/10.1002/onco.13739

Table 1. Immune checkpoint inhibitor indications

Melanoma; adjuvant, unresectable, or metastatic
Non-small cell lung cancer; metastatic
Small cell lung cancer; metastatic
Hepatocellular carcinoma
Renal cell carcinoma; advanced, or metastatic
Hodgkin lymphoma
Head and neck squamous cell carcinoma; recurrent or metastatic
Urothelial carcinoma; locally advanced or metastatic
Breast cancer; triple-negative locally advanced or metastatic
Colon cancer, metastatic (MSI-H or dMMR)
Glioblastoma
Cutaneous squamous cell carcinoma; locally advanced or metastatic
Gastric cancer; recurrent locally advanced or metastatic
Anal cancer; metastatic
Merkel cell carcinoma
Primary mediastinal large B-cell lymphoma
Mesothelioma

Abbreviations: dMMR mismatch repair deficient; MSI-H, microsatellite instability-high.

HCV. In this article, we conducted a retrospective study of all patients with cancer with HCV untreated and resolved who received ICI at our institution.

Materials and Methods

This was a single-institution retrospective electronic chart review of all patients with active or resolved hepatitis C viral infection who were treated with an immune checkpoint inhibitor (ICI) for cancer of any type and stage from January 2012 to December 2019. Data collected included age, gender, ethnicity, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status at the time of cancer diagnosis, cancer type and stage, hepatitis C status (specified as untreated chronic infection if the viral load was detected at the time of cancer diagnosis, treated if a history of treatment with undetectable viral load was documented, and spontaneously resolved if only hepatitis C virus antibody was present with undetectable viral load and absence of treatment history), viral genotype, presence of cirrhosis, liver function test before and throughout treatment, type of ICI, length of therapy in weeks, the reason for discontinuation of therapy, and toxicities. Patients with coinfection with hepatitis B virus or human immunodeficiency virus were excluded. The severity of immune-mediated toxicities was graded using National Cancer Institute CTCAE, Version 5.0 [3]. The study was approved by the institutional review board.

Results

We identified 40 cases, 30 (75%) men and 10 (25%) women, with median age of 64 years (range, 51–80). The largest ethnicity was Black (22; 55%), followed by White (17; 42.5%)

Table 2. Characteristics of patients with HCV with adverse events while on immune checkpoint inhibitors

Case	Age, years	Sex	Ethnicity	ECOG PS	Cancer	HCV status	Genotype	Viral Load	Cirrhosis	Therapy	Length of therapy, weeks	Reason for discontinuation	Toxicities
1	65	M	Black	0	NSCLC	Untreated	1a	385×10^3	No	Nivolumab	78	Toxicities	Pneumonitis, grade 3
2	61	F	Black	1	NSCLC	Untreated	1a	744×10^3	No	Nivolumab	5	PD	Fatigue grade, 1
3	64	F	Black	0	NSCLC	Treated	1a	0	No	Nivolumab and ipilimumab	24	Ongoing	Hypothyroidism, grade 1 and fatigue, grade 2
4	55	F	White	1	SCLC	Untreated	1a	152×10^3	No	1	9	Toxicities	Colitis, grade 3
5	74	F	Other	1	HCC	Treated	1a	0	Yes	Nivolumab	25	PD	Fatigue, grade 1
6	66	M	White	0	HCC	Untreated	1a	557×10^3	Yes	Nivolumab	12	PD	Hepatotoxicity, grade 1
7	59	M	Black	1	HCC	Untreated	1b	$3{,}190 \times 10^3$	Yes	Nivolumab	16	PD	Hepatotoxicity, grade 2

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance Status; F, female; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; M, male; NSCLC, non-small cell lung cancer; PD, progressive disease; SCLC, small cell lung cancer.

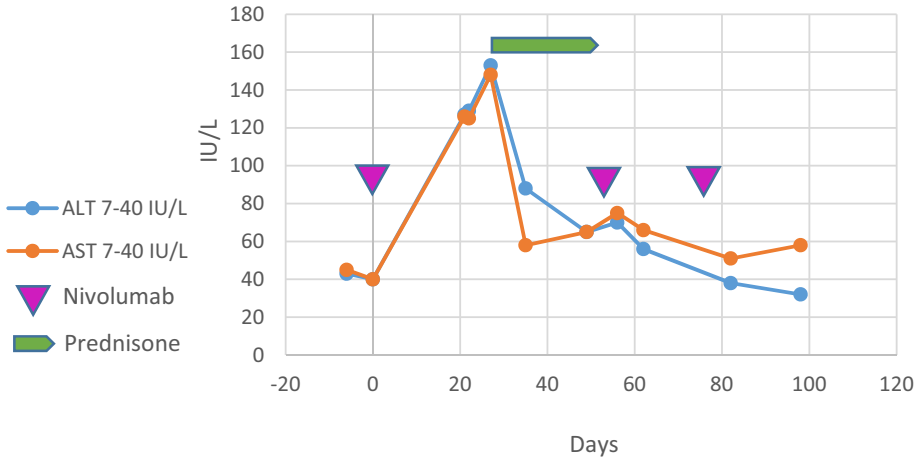

Figure 1. Timeline of the patient with grade 2 hepatotoxicity due to nivolumab.
Abbreviations: ALT alanine transaminase; AST aspartate transaminase.

and others (1; 2.5%). ECOG was 0–1 in 36 patients (90%) and 2 in four patients (10%). Median BMI was 24.3 kg/m^2 (range, 16.7–42.8). Cancer types were non-small cell lung cancer (18; 45%), hepatocellular carcinoma (12; 30%), head and neck cancer (4; 10%), small cell lung cancer (3; 7.5%), renal cell carcinoma (1; 2.5%), colon cancer (1; 2.5%), and melanoma (1; 2.5%). Hepatitis C was untreated in 17 patients (42.5%), treated in 14 patients (35%), and spontaneously resolved in 9 (22.5%) patients. Hepatitis C genotype was 1a in 25 patients (62.5%), 1b in 1 patient (2.5%), 3 in 1 (2.5%) patients, and unavailable for the rest. Viral load in untreated patients ranged from 45 to 7,620 $\times$ 10^3 copies per mL. Cirrhosis was documented in 22 patients (55%). None of the untreated patients received treatment for HCV at the time of cancer diagnosis before the commencement of ICI. ICIs used were nivolumab alone in 23 patients (57.5%), pembrolizumab in 10 (25%), atezolizumab in 4 (10%), durvalumab in 2 (5%), and combination of ipilimumab and nivolumab in 1 (2.5%). The median length of therapy with ICI was 16 weeks (range, 2–199). AEs noted (see Table 2) were grade 3 pneumonitis in one patient (2.5%) on pembrolizumab, grade 3 colitis in one patient (2.5%) on nivolumab, hepatotoxicity in two patients (5%) on nivolumab (one patient with grade 1 and the other had grade 2), grade 1–2 fatigue in three patients (7.5%), and hypothyroidism in one patient (2.5%).

The patient with grade 2 hepatotoxicity was a 55-year-old African American man with HCC. He had liver cirrhosis with MELD score of 7, ascites, and HCV with genotype 1b. The hepatotoxicity occurred after the first dose of nivolumab. Hepatotoxicity was marked by transaminitis, whereas alkalyine phosphatase, bilirubin, albumin, and clotting factors remained within the normal range. He was treated with prednisone 1 mg/kg with a taper over 2 weeks with a return of liver function test to baseline. He was continued on nivolumab with no further recurrence of hepatotoxicity, for timeline, and degree of transaminitis (see Fig. 1).

Discussion

Chronic hepatitis C infection is a major health problem, with a prevalence of approximately 1% in the U.S., with higher rates in states with a worse opioid crisis, likely owing to increased injection drug use [4]. Although effective therapy for HCV is now present, challenges in prevention, case detection, treatment affordability, and access propose that HCV burden will continue to be a significant health care issue in the foreseeable future [4]. Population-based studies concerning cancer risk in HCV-infected patients showed an increased risk for hepatocellular carcinoma, non-Hodgkin lymphoma, and lung cancer [5, 6]. Along with the expanding indications for ICI, the coexistence of HCV and potentially ICI-responsive cancer will be encountered more frequently. Two landmark trials that studied PD-1 inhibitors in hepatocellular carcinoma included treated and untreated HCV patients: a phase I–II study of nivolumab in hepatocellular carcinoma included 50 patients with HCV, CheckMate-40 (NCT01658878), and a phase II study of pembrolizumab in hepatocellular carcinoma that included 26 patients with HCV, Keynote-224 (NCT02702414) [7, 8]. However, trials investigating ICIs in cancers other than hepatocellular carcinoma have excluded patients with HCV infection, as it is unknown how the ICIs will interplay with the underlying chronic infection (e.g., the potential for a flare of chronic HCV infection or higher rate of AEs).

In this article, we report our case series of 40 patients covering the past 8 years addressing the safety of ICIs in patients with HCV. The predominance of men in our study may be explained by predominant tumor subtypes in our cohort, namely, non-small cell lung cancer and hepatocellular carcinoma, both of which are more common in men, which is likely attributed to an increased likelihood of adapting high-risk behaviors in men that increase their risk for these cancers (e.g., smoking and injectable drug use) [6, 9]. Ethnicities reported were reflective of the background population [10].

In our study, PD-1/PD-L1 inhibitor AE rates were comparable to those reported in clinical trials that excluded 1%–3% of patients with HCV [11, 12]. No deaths related to ICI were identified. Only two patients suffered grade 3 AEs: one with colitis on nivolumab and another with pneumonitis on pembrolizumab, with resultant discontinuation of treatment in both. There were only two cases of hepatotoxicity, with

the worst being grade 2 in a patient with genotype 1b; however, the patient was able to continue ICI following glucocorticoid course. Both patients with hepatotoxicity had hepatocellular carcinoma, untreated HCV, and liver cirrhosis and were treated with nivolumab. Viral load was not checked at the time of liver enzyme derangement; therefore, it is not possible to comment if an HCV flare was contributing. In the aforementioned trials of PD-1 inhibitors in hepatocellular carcinoma, CheckMate-40 and Keynote-224, no HCV flares were reported [7, 8].

Study limitations include single-center study and all the limitations of a retrospective design; selection bias and lack of rigorousness in documenting all possible treatment toxicities compared with a prospective study. The majority of patients were male, and the prevailing genotype was 1a. HCV genotype varies racially and geographically; therefore, our findings may not be generalizable [13]. Interestingly, the patient with grade 2 hepatotoxicity had HCV genotype 1b, which was under-represented in our cohort. Further studies, including all HCV genotypes, are needed to evaluate if certain genotypes carry a higher risk of ICI-related AEs. Other areas of study include characterization of PD-L1 expression in the liver and its effect on AE rates, the safety of ICIs in patients with HCV coinfected with hepatitis B virus and/or human immunodeficiency virus, and cancer registry studies to explore possible health disparities should patients with HCV and cancer be less likely to receive ICI.

Conclusion

In the lack of randomized controlled trials to address the safety of ICI in HCV and other major chronic viral infections across different cancers, observational studies may help to illustrate if such populations tend to have higher rates of ICI AEs. This observational study showed no deaths related to ICIs, and AE profiles in untreated and resolved patients with HCV were comparable to rates of non-HCV patients. ICI was not delayed in our cohort pending treatment for active HCV. These findings may aid the oncologist in discussing ICI toxicities in patients with cancer with untreated and resolved HCV.

Author Contributions

Conception/design: Akram Alkrekshi, Ila Tamaskar
Provision of study material or patients: Akram Alkrekshi, Ila Tamaskar
Collection and/or assembly of data: Akram Alkrekshi, Ila Tamaskar
Data analysis and interpretation: Akram Alkrekshi, Ila Tamaskar
Manuscript writing: Akram Alkrekshi, Ila Tamaskar
Final approval of manuscript: Akram Alkrekshi, Ila Tamaskar

Disclosures

The authors indicated no financial relationships

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