ORIGINAL ARTICLE

Immune Checkpoint Inhibitors in Patients With Cancer and Infection by Hepatitis B or C Virus: A Perspective Through the Results of a European Survey

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ABSTRACT

Introduction: Patients with cancer and hepatitis B virus (HBV) or hepatitis C virus (HCV) infection are underrepresented in several clinical trials testing immune checkpoint inhibitors (ICIs). Consequently, safety and efficacy of ICI therapy in this population have not been completely defined. We aimed to evaluate the attitudes of oncologists on this topic.

Methods: We conducted a 14-item European anonymous online survey.

Results: Physicians from 56 oncology departments (26 from Italy, 15 from France, and 15 from Spain) took part in the survey. They mainly used to prescribe ICIs for treating patients with lung cancer, melanoma, and renal cell carcinoma. Of them, 95% recognized the need for specific guidelines addressing the management of patients with

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cancer and HBV or HCV treated with ICIs. Just 63% of the respondents screened patients for HBV and HCV status before ICIs initiation, although the risk of immune-related hepatotoxicity or viral reactivation was a major concern for most of them. Only 9% of the surveyed oncologists considered HBV and HCV infection a major exclusion criterion for receiving ICIs. Furthermore, 29% of the respondents would start a prophylactic treatment of active infection at ICIs initiation.

Conclusions: ICIs administration in patients with cancer and HBV or HCV infection is of concern for most of the surveyed European oncologists. Nonetheless, active screening and treatment of viral hepatitis should be improved. Data in this specific setting are needed for an evidence-based management and should be generated by broadening inclusion criteria of clinical trials to allow the enrollment of patients with HBV and HCV.

Keywords: Immune checkpoint inhibitors; Cancer; HBV; HCV; Immunotherapy; Viral hepatitis

Introduction

Immune checkpoint inhibitors (ICIs) have a relevant role for the treatment of a wide spectrum of cancer types, both as monotherapy or in combination strategies.[1]

Nevertheless, some special populations, such as patients with autoimmune disease, with organ transplantation, undergoing immunosuppressive treatments, or with human immunodeficiency virus, hepatitis B virus (HBV), and hepatitis C virus (HCV), have usually been excluded from many clinical trials testing ICI agents.[2,3] As a result, the safety and efficacy of ICIs in these clinical situations remain partially unknown, making it difficult to set up an evidence-based approach in daily clinical practice.

Estimates of seroprevalence of these agents in the European general population can significantly vary according to the geographical area, ranging from 0.1% to 4.4% for HBV and from 0.1% to 5.9% for HCV.[4] The epidemiologic scenario of HBV and HCV infection among patients with cancer is moreover depending on tumor type. Some studies reported detection of HBV surface antigen (HBsAg) in 4.4% to 5.3% of patients with solid tumors, whereas HCV infection has been observed in 1.5% to 10.6% of patients with nonhematologic tumors other than hepatocellular carcinoma (HCC) and in up to 30% of patients with blood cancers. A U.S. study cohort assessed the virologic status of 3051 patients with a newly diagnosed solid or hematologic tumor. The prevalence of a resolved HBV was 5.3%, whereas the prevalence of a chronic infection by HCV or HBV was 1.9% and 0.4%, respectively. When focusing on lung cancer, these rates raised to 8.7%, 0.6%, and 4.9%, respectively.[5–11] It is worth of note that HBV reactivation has been reported in up to 68% of patients treated with chemotherapy and immunosuppressive treatments.[12] This serious complication is linked to an increased risk of morbidity and mortality.[12,13]

Anticancer immunity, ICIs-induced immune response, and chronic infections represent different sides of a composite and complex system. A chronic viral infection occurring concomitantly to an ICI treatment could potentially interfere at the same time with the anticancer immune response and viral clearance.[2] To date, limited evidence exists on this regard. A nonnegligible HBV reactivation rate was observed among patients with cancer with positive HBsAg treated with anti programmed cell death protein 1.[14] In contrary, no cases of HBV or HCV flare were observed in the phase 3 KEYNOTE-240 trial in patients with HCC treated with pembrolizumab.[15] Immune-related hepatitis, however, occurred only in patients within the immunotherapy arm. Furthermore, in contrary, it has been postulated that ICIs might even restore the adaptive immunity against HBV and HCV in chronically infected patients, leading to a viral clearance.[16] Nevertheless, a limited and short-duration antiviral activity was observed in the CheckMate-040 trial among patients with advanced HCC and HCV infection treated with nivolumab.[17]

The lack of specific data in this setting may have an impact on therapeutic decisions and ICIs prescription in clinical routine. We therefore conducted a European survey among oncologists to evaluate which are the attitudes toward the management of ICIs for the treatment of patients with cancer and HBV or HCV.

Material and Methods

An anonymous virtual 14-item survey (see Supplementary Material) was sent by means of direct e-mail invitation to representatives of oncological centers in Italy, France, and Spain up to January 2020. The survey was promoted by the Sociedad Española de Oncología Médica and by the European Organization for Research and Treatment of Cancer Lung Cancer Group members.

Study Objectives and Characteristics of the Survey

The survey aimed at investigating the attitudes of European oncologists toward the management of ICIs to treat patients with cancer and HBV or HCV infection. It

was designed by both oncologists and an infectious disease specialist. The investigated areas were: (1) the perception of risks associated with the use of ICIs in patients with cancer and HBV or HCV infection; (2) the assessments of HBV and HCV status in patients with cancer, candidates to ICI therapy; (3) the choice whether to treat with ICIs patients with cancer and HBV or HCV infection; and (4) the management of ICI therapy in patients with cancer and HBV or HCV infection.

Statistical Analysis

On the basis of the descriptive nature of the survey, no sample size was preplanned. The estimated margin of error with a 95% confidence level would have been 13% with a number of respondents of 50. Analyses were mainly descriptive. Fisher's exact test or chi-square test was applied to evaluate categorical variables. Tests were two sided, and p value less than 0.05 was considered statistically significant.

Results

A complete detail of the responses given to each question is reported in the Appendix, with answers reported for each single country and as total. The survey was answered by representatives of 56 European oncological centers (26 from Italy, 15 from France, 15 from Spain). Most of the respondents from Italy (56%) and France (80%) worked in oncology units that had treated with ICIs at least 100 patients outside of clinical trials, whereas only 26.7% from Spain did ($p = 0.013$). Most of the oncologists who answered the survey used to treat with ICIs patients with lung cancer, melanoma, and renal cell carcinoma and less frequently with head and neck, urothelial cancer, and HCC. Table 1 summarizes these characteristics.

Table 1. Characteristics of the Practicing Centers of Surveyed Oncologists

Characteristic	n (%)
Country	
Italy	26 (46)
France	15 (27)
Spain	15 (27)
Number of patients already treated with ICIs	
<50	15 (27)
51-100	10 (18)
101-150	7 (12)
>150	24 (43)
Estimated distribution of patients treated with ICIs by cancer type, %	
Lung cancer	35
Melanoma	21
Renal cell carcinoma	15
Head and neck cancer	11
Urothelial cancer	9
Hepatocellular carcinoma	5
Others	4

ICIs, immune checkpoint inhibitors.

The Perception of Risks Associated With the Use of ICIs in Patients With Cancer and HBV or HCV Infection

Almost all the respondents (95%) recognized the need for specific guidelines on the management of ICI therapy in patients with HBV or HCV. In addition, 61% of the respondents declared to be concerned of treating with ICIs patients with an active viral hepatitis (i.e., detectable HBsAg, HBV-DNA or HCV-RNA), but to have considered to do it in selected cases. Only 9% of the oncologists considered an active viral infection as a major exclusion criterion for receiving ICIs (Fig. 1), with no difference according to countries ($p = 0.315$).

The most frequent reasons of concern were the potential reactivation of HBV or HCV infection and the potential increased risk of immune-related hepatotoxicity requiring immunotherapy discontinuation.

The Assessment of HBV and HCV Status in Patients With Cancer Candidates to ICI Therapy

Only 63% of the centers screened for HBV and HCV infection before ICIs initiation (Fig. 2), and this finding was consistent between different countries ($p = 0.738$). Moreover, the serologic tests performed (research of viral antigens, antivirus antibodies, viral nucleic acids) were heterogeneous (see Appendix). We did not find any statistical difference in screening attitude according to the volume of patients treated in each center ($p = 0.345$), even if the rate of systematic screening was numerically increased in biggest centers as compared with those with less experience in managing ICIs (75% versus 47%) (Supplementary Fig. 1). In addition, we observed that among physicians not routinely performing a screening for HBV and HCV (n = 21), no one declared to be afraid of the clinical scenario after a positive test result to the point of avoiding ICI therapy. In contrary, 14% (n = 5) of the respondents who used to screen considered an active infection as a major contraindication to ICIs administration (Supplementary Table 1).

The Choice Whether to Treat With ICIs Patients With Cancer and HBV or HCV Infection

Although 64% of the respondents declared to always treat patients with cancer with ICIs in case of a past HBV (i.e., positive anti-HBc, positive anti-HBs) or HCV (i.e., positive anti-HCV, undetectable HCV-RNA) infection, in 34% of cases, this decision was taken individually. This attitude was similar in all countries ($p = 0.269$).

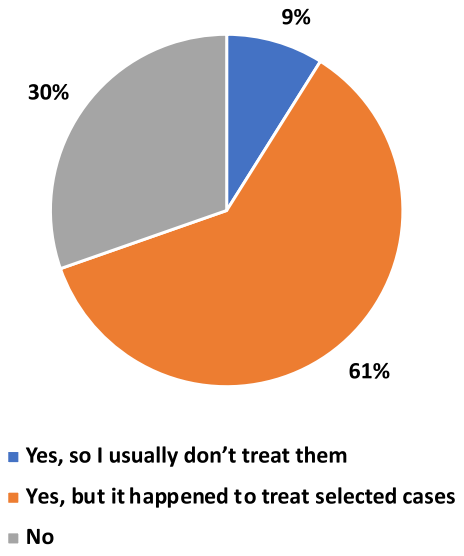

Figure 1. Perception on immunotherapy administration to patients with active viral hepatitis. Question: Are you usually afraid of treating with ICIs patients with solid tumor and active HBV or HCV infection? (active HBV infection = positive HBsAg or detectable HBV-DNA, negative anti-HBs; active HCV infection = detectable HCV-RNA). HB, hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor.

More than half of the respondents reported not having always treated with immunotherapy patients with solid tumor and active HBV or HCV (i.e., detectable HBsAg, HBV-DNA or HCV-RNA) (see Appendix). No difference between countries was observed.

Physicians who used to treat the infection when detected were more likely working in centers with greater experience in ICI therapy than physicians who did not usually have this attitude (69% versus 33%) and were more predisposed to routinely do screening for HBV and HCV before immunotherapy initiation (75% versus 56%) (Supplementary Table 2).

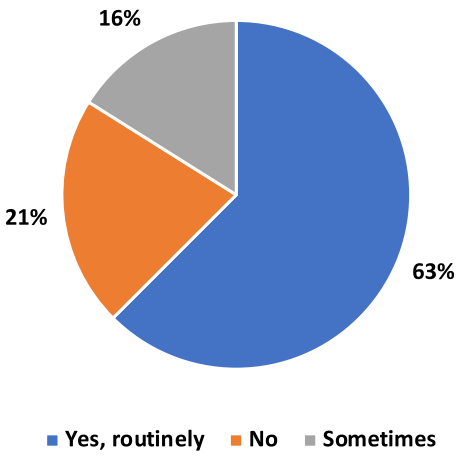

Figure 2. Screening attitude for HBV and HCV infection. Question: Do you usually test for HBV and HCV status before starting a treatment with ICIs? HBV, hepatitis B virus; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor.

The Management of ICI Therapy in Patients With Cancer and HBV or HCV Infection

Overall, 77% of the oncologists referred patients with cancer and active HBV or HCV to the infectious disease specialist or hepatologist when starting an ICI treatment. Nevertheless, 14% of the respondents only referred the patient in case of a chronic viral disease and transaminase level elevation.

In 70% of the centers, a prophylactic antiviral treatment was not administered under immunotherapy in patients with chronic viral infection, but only a monitoring of laboratory parameters was usually performed (transaminase and HBV-DNA or HCV-RNA, periodically or at the occurrence of hepatitis flare). Only 29% of the respondents indeed declared to prophylactically treat the infection (Fig. 3). No difference between countries was observed on this approach ($p = 0.255$).

Discussion

We have reported the perception, concerns, and attitudes of oncologists from three European countries about the management of immunotherapy in patients with cancer and HBV or HCV infection. Although the risk of immune-related adverse events (irAEs) and viral reactivation was considered a major concern, only 63% of the respondents performed the HBV and HCV status screening at baseline and only one-third of the respondents would start an antiviral prophylaxis in the event of a chronic infection at ICIs introduction.

Similarly to our findings, in a large cohort study conducted in the U.S. which aimed to determine the HBV and HCV status of patients with newly diagnosed cancer, up to 42% of cases of chronic viral hepatitis were not previously known.[5] Globally, this point highlights the potential underdiagnosis of these high-prevalent infections in European citizens[4] and the importance of screening patients with a diagnosis of cancer to prevent the risks associated to a viral reactivation and potential irAEs.

Actually, international guidelines recommend screening for HBV by HBsAg, anti-HBc (total immunoglobulin or IgG), and anti-HBs all patients before starting systemic anticancer therapies, including immunotherapy.[18,19] Ruling out occult infections is also important in case of administration of corticosteroids and immunosuppressive agents to limit irAEs.[20] Screening strategy for hepatitis C is less harmonized and limited by the fact that a positive anti-HCV test result could not differentiate active from resolved infection, so that a confirmatory HCV-RNA test is needed. Currently, it is considered that all patients with cancer should be screened for HCV.[5,10,19,21]

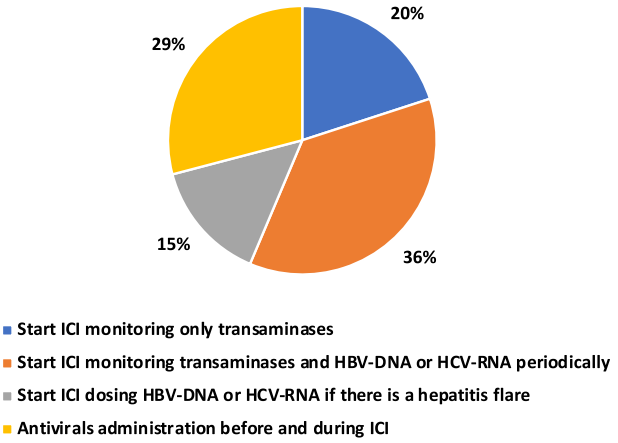

Figure 3. Management of viral infection in patients with cancer treated with immunotherapy. Question: How do you usually manage patients with active HBV or HCV infection treated with ICIs? HBV, hepatitis B virus; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor.

Nonetheless, screening recommendations in oncology are relatively recent and do not follow what is worth in the general population, where indications are age and risk adapted.[19] We have also observed that the attitude to routinely screen is related to the attitude in managing cases tested with positive result because probably the less is perceived the clinical impact of a viral infection, the less is felt the importance of testing.

Regarding the risk of toxicity, a systematic review and meta-analysis that collected data of 186 patients with advanced-stage cancer and infection by HBV (n = 89), HCV (n = 98), or both (n = 1), treated with ICIs (as a single agent or in combination between them), reported an increase in the viral load in 2.8% of cases; the rate of grade greater than or equal to 3 transaminase elevation was instead 3.4% and 17.3% in HBV- and HCV-infected patients, respectively.[22] The incidence of grade greater than or equal to 3 immune-related hepatitis was 12% in one of the largest retrospective cohort of patients with HBV or HCV treated with ICIs for advanced-stage solid tumors.[23] Moreover, among 114 HBsAg-positive patients treated with anti programmed cell death protein 1, a HBV reactivation rate of 5.3% was observed, which raised to 17.2% among patients not receiving an antiviral prophylaxis. In this study, the absence of antiviral prophylaxis was the only relevant risk factor for HBV reactivation (odds ratio = 17.50).[14]

The underrepresentation of patients with HBV or HCV in clinical trials with ICIs has led to a lack of prospective evidence on this topic, so currently data are mainly derived from case series and retrospective cohorts.[19,22,23] In fact, many clinical trials incorporating ICIs as part of the study plan have so far required to screen for active infection and exclude from the enrollment those positive patients. Despite this, in our survey, almost all the respondents did not consider ICI therapy contraindicated in patients with a past infection, thus being in line with international recommendations.[18] Nevertheless, one point for improvement is the prophylactic treatment of active infections. Patients with chronic HBV should receive an antiviral prophylactic therapy through and for at least 6 to 12 months after a systemic anticancer treatment. Monitoring recommendations include checking transaminases and HBV-DNA during anticancer and antiviral therapies. An adequate hepatologic assessment including patients' history, physical examination, blood tests, and viral-induced disease burden is also advised.[18,24] The risk of HBV reactivation after clinically resolved infection depends on different variables, related to the virus, the host, the underlying disease, and the anticancer treatment. A prophylaxis may not be systematically required in patients with undetectable viral load and positive anti-HBs.[19] With respect to the management of HCV, direct-acting antiviral agents (DAAs) may effectively prevent potential infection-related complications, owing to a high efficacy leading to obtain a virologic response in more than 90% of cases.[3,25] Despite not being supported by randomized clinical trials, expert consensuses consider that the overall benefits of DAAs outweigh the risks of not treating HCV infection.[19] DAAs became available in Europe in 2014, at the beginning with a prioritized access policy, but afterward pan-genotypic drugs granted a universal access.[26,27] At the time this survey was run, there were no major barriers to their use. Similarly, no limits to availability and reimbursement of HBV drugs could be called into question.[28] Nevertheless, although data support expanding therapy coverage in the general population irrespective of the liver damage caused by the infection,[29,30] it should be acknowledged that long-term benefit could sometimes not exceed costs of treatment in patients with cancer, particularly in the metastatic setting. Moreover, physicians are not supported in their practice by dedicated strategies on how managing drugs for HBV and HCV in immuno-oncology setting.[21] We have indeed tracked that the attitude to treat a detected infection is more pronounced in centers with more experience in managing ICI therapy, so that promoting targeted educational interventions could be of use.

Although limited by the small sample size, this analysis captured the most relevant concerns and attitudes of oncologists regarding the management of viral hepatitis in patients receiving ICIs, particularly in three countries with similar patterns of immunotherapy access and prescription. We did not investigate which treatment strategies would have been adopted as alternative to the use of ICIs in patients considered not suitable to

receive this therapy, because these would be based on a case-by-case evaluation taking into account performance status, clinical profile, tumor type, and tumor molecular characteristics. Moreover, precise reasons behind attitudes toward the management of HBV and HCV in patients receiving ICIs were not exhaustively assessable.

Universal adult vaccination for HBV and interventions in subjects at higher risk for viral hepatitis are reducing the burden of these infections in the general population, and as a consequence potentially also the perception around risks associated with active viral hepatitis in oncology population. Education on this theme, contact with dedicated facilities, and financial costs may be determinants and thus areas of intervention in this setting. Overall, a risk-benefit balancing assessment and a proper multidisciplinary management of patients with cancer and viral hepatitis are crucial to reduce the occurrence of negative adverse events by preserving resources and sparing the patient avoidable additional medications.[19,31]

In conclusion, this study has evaluated the clinical practice of oncologists with regard to the management of ICIs to treat patients with concurrent viral hepatitis. Some areas of improvement have emerged, particularly concerning the attitude to systematically screen the virologic status in patients with cancer and to treat the viral infection when immunotherapy agents are administered. The results of our survey call attention on the need to draw evidence-based approaches to this topic and to broaden the enrollment of patients with HBV or HCV in oncology clinical trials with ICIs, to fill the gap of knowledge that has been due, to date, to their exclusion. Safety and efficacy of ICIs in this setting should be gradually investigated by means of multicentric retrospective studies and proper tailored indication to manage viral hepatitis cases within clinical trials. Paradigm shift in oncology thanks to the advent of immunotherapy should forcedly be followed by redesign on handling challenging clinical situations.

CRediT Authorship Contribution Statement

Marco Tagliamento: Conceptualization, Methodology, Data curation, Project administration, Writing (original draft, review and editing).

Jordi Remon: Project administration, Writing (original draft, review and editing).

Matteo Giaj Levra: Project administration, Writing (review and editing).

Andrea De Maria: Methodology, Writing (review and editing).

Paolo Bironzo: Conceptualization, Methodology, Writing (original draft, review and editing).

Benjamin Besse: Supervision, Writing (review and editing).

Silvia Novello: Supervision, Writing (review and editing).

Laura Mezquita: Conceptualization, Supervision, Writing (original draft, review and editing).

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at 10.1016/j.jtocrr.2022.100446.

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