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Immune checkpoint inhibitors in patients with cancer and infection by hepatitis B or C virus: a perspective through the results from a European survey

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KEYWORDS: immune checkpoint inhibitors; cancer; hepatitis B; hepatitis C; HBV; HCV; immunotherapy
ABBREVIATIONS

ICIs: immune checkpoint inhibitors
HIV: human immunodeficiency virus
HBV: hepatitis B virus
HCV: hepatitis C virus
HBsAg: hepatitis B surface antigen
PD-1: programmed death protein-1
HCC: hepatocellular carcinoma
SEOM: Sociedad Española de Oncología Médica
EORTC: European Organisation for Research and Treatment of Cancer
anti-HBc: anti-hepatitis B core antibodies
irAEs: immune-related adverse events
DAA: direct-acting antiviral agents
ABSTRACT

**Background:** Patients with cancer and hepatitis B virus (HBV) or C virus (HCV) infection are underrepresented in several clinical trials testing immune checkpoint inhibitors (ICIs). Consequently, safety and efficacy of ICIs therapy in this population have not been completely defined. We aimed to assess 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 to the survey. They mainly used to prescribe ICIs for treating patients with lung cancer, melanoma and renal cell carcinoma. 95% of them recognized the need for specific guidelines addressing the management of patients with cancer and HBV/HCV infection treated with ICIs. Just 63% of the respondents screened patients for HBV/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/HCV infection a major exclusion criterion for receiving ICIs. 29% of the respondents would start a prophylactic treatment of active infection at ICIs initiation.

**Conclusions:** ICIs administration in patients with cancer and HBV/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/HCV infection.
1. 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 diseases, organ transplantation, those undergoing immunosuppressive treatments, or with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, have usually been excluded from many clinical trials testing ICIs agents 2,3. As a result, the safety and the 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 epidemiological scenario of HBV/HCV infection among patients with cancer is moreover depending on tumor type. Some studies reported detection of Hepatitis B surface antigen (HBsAg) in 4.4%-5.3% of patients with solid tumors, while HCV infection has been observed in 1.5% to 10.6% of patients with non-hematologic tumors other than hepatocellular carcinoma (HCC), and in up to 30% of patients with blood cancers 5. A US study cohort assessed the virological status of 3,051 patients with a newly diagnosed solid or hematologic tumor. The prevalence of a resolved HBV was 5.3%, while 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 rate 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 a ICIs treatment could potentially interfere at the same time with the anticancer immune response as well as with the viral clearance. To date, limited evidence exists on this regard. A non negligible HBV reactivation rate was observed among patients with cancer with positive HBsAg treated with anti-programmed death protein-1 (PD-1). On the contrary, no cases of HBV/HCV flare were observed in the phase III KEYNOTE-240 trial in patients with HCC treated with pembrolizumab. However, immune-related hepatitis occurred only in patients within the immunotherapy arm. On the contrary, it has also been postulated that ICIs might even restore the adaptive immunity against HBV and HCV in chronically infected patients, leading to a viral clearance. Nevertheless, a limited and of short duration antiviral activity was observed in the CheckMate 040 trial among patients with advanced HCC and HCV infection treated with nivolumab. The lack of specific data in this setting may has an impact on therapeutic decisions and ICIs prescription in clinical routine. We therefore conducted a European survey among oncologists, in order to assess which are the attitudes towards the management of ICIs for the treatment of patients with cancer and HBV/HCV infection.

2. MATERIAL AND METHODS

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

2.1 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/HCV infection. It was designed by both oncologists and infectious diseases specialist. The investigated areas were: i) the perception of risks associated with the use of ICIs in patients with cancer and HBV/HCV infection; ii) the assessments of HBV/HCV infection status in patients with cancer candidates to ICIs therapy; iii) the choice whether to treat with ICIs patients with cancer and HBV/HCV infection; iv) the management of ICIs therapy in patients with cancer and HBV/HCV infection.

2.2 Statistical analysis
Based on the descriptive nature of the survey, no sample-size was pre-planned. 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 exact test or Chi Square test were applied to evaluate categorical variables. Tests were 2-sided, and p < 0.05 was considered statistically significant.

3. RESULTS
A complete detail of the responses given to each question is reported in the Appendix, with answers reported for each single county 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, while only 26.7% from Spain did (p = 0.013). The majority of the oncologists who answered the survey used to treat with ICIs patients with lung cancer, melanoma and renal cell carcinoma, while less frequently head and neck, urothelial and hepatocellular carcinoma. Table 1 summarizes these characteristics.

3.1 The perception of risks associated with the use of ICIs in patients with cancer and HBV/HCV infection
Almost all the respondents (95%) recognized the need for specific guidelines on the management of ICIs therapy in patients with HBV/HCV infection. 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 HBV/HCV infection as a major exclusion criterion for receiving ICIs (Figure 1), with no difference according to countries (p = 0.315).

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

3.2 The assessment of HBV/HCV infection status in patients with cancer candidates to ICIs therapy

Only 63% of the centers screened for HBV/HCV infection before ICIs initiation (Figure 2), and this finding was consistent between different countries (p = 0.738). Moreover, the serological tests performed (research of viral antigens, anti-virus 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 to those with less experience in managing ICIs (75% vs. 47%) (Figure 1). In addition, we observed that among physicians not routinely performing a screening for HBV/HCV infection (n=21), no one declared to be afraid of the clinical scenario following a positive test to the point of avoiding ICIs therapy. On the contrary, 14% (n=5) of the respondents who used to screen, considered an active infection as a major contraindication to ICIs administration (Table 1).

3.3 The choice whether to treat with ICIs patients with cancer and HBV/HCV infection

While 64% of the respondents declared to always treat patients with cancer with ICIs in case of a past HBV (i.e., positive anti-hepatitis B core antibodies [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).

More than half of the respondents reported not having always treated with immunotherapy patients with solid tumor and active HBV or HCV infection (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 ICIs therapy than physician you did not usually do that (69% vs. 33%) and were more predisposed to routinely do screening for HBV/HCV before immunotherapy initiation (75% vs. 56%) (Table 2).

3.4 The management of ICIs therapy in patients with cancer and HBV/HCV infection

Overall, 77% of the oncologists referred patients with cancer and active HBV/HCV infection to the infectious disease specialist or hepatologist when starting a ICIs treatment. However, 14% of the respondents only referred the patient in case of a chronic viral disease and transaminases elevation.

In 70% of the centers a prophylactic antiviral treatment was not administered under immunotherapy in patients with chronic HBV/HCV infection, but only a monitoring of lab parameters was usually performed (transaminase and/or 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 (Figure 3). No difference between countries was observed on this approach (p = 0.255).

4. 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/HCV infection. Although the risk of immune-related adverse events (irAEs) and HBV/HCV reactivation was considered a major concern, only 63% of the respondents performed the HBV/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 ICl s introduction.

Similarly to our findings, in a large cohort study conducted in the US that aimed to determine the HBV/HCV infection status of patients with newly diagnosed cancer, up to 42% of cases of chronic viral hepatitis were not previously known. Globally, this point highlight the potential underdiagnosis of these high prevalent infections in European citizens, as well as the importance of screening patients at the 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 immunoglobulin (total or IgG), and HBsAb all patients before starting systemic anticancer therapies, including immunotherapy. Ruling out occult infections is also important in case of administration of corticosteroids and immunosuppressive agents to limit irAEs. Screening strategy for hepatitis C is less harmonized and limited by the fact that a positive anti-HCV test 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 infection.

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. We have also observed that the attitude to routinely screen is related to the attitude in managing cases tested positive, since 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 single agent or in combination between them), reported an increase in the viral load in 2.8% of cases; the rate of grade ≥3 transaminases elevation was instead 3.4% and 17.3% in HBV and HCV infected patients, respectively. The incidence of grade ≥3 immune-related hepatitis
was 12% in one of the largest retrospective cohort of patients with HBV and/or HCV infection treated with ICIs for advanced stage solid tumors. Moreover, among 114 HBsAg-positive patients treated with anti-PD-1, an HBV reactivation rate of 5.3% was observed, that raised to 17.2% among patients not receiving an antiviral prophylaxis. In this study, the absence of antiviral prophylaxis was the only significant risk factor for HBV reactivation (odds ratio 17.50).

The underrepresentation of patients with HBV/HCV infection 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. 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 ICIs therapy contraindicated in patients with a past infection, thus being in line with international recommendations. However, one point for improvement is the prophylactic treatment of active infections. Patients with chronic infection should receive an antiviral prophylactic therapy through and for at least 6-12 months following a systemic anticancer treatment. Monitoring recommendations include checking transaminases and HBV-DNA during anticancer and antiviral therapy. An adequate hepatological assessment including patients history, physical exam, blood tests and viral-induced disease burden is also advised. 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. With respect to the management of HCV infection, direct-acting antiviral agents (DAAs) may effectively prevent potential infection-related complications, due to a high efficacy leading to obtain a virologic response in more than 90% of cases. 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. DAAs became available...
in Europe in 2014, at the beginning with a prioritized access policy, but afterwards 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, while 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 HBV/HCV drugs in immuno-oncology setting \(^{31}\). We have indeed tracked that attitude to treat a detected infection is more pronounced in centers with more experience in managing ICIs 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, since these would be based on a case-by-case evaluation taking into account performance status, clinical profile, histology and tumor molecular characteristics. Moreover, precise reasons behind attitudes toward the management of HBV/HCV in patients receiving ICIs were not exhaustively assessable. Universal adult vaccination for hepatitis B 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 is
crucial to reduce the occurrence of negative adverse events but preserving resources and sparing the patient avoidable additional medications\textsuperscript{19,31}.

5. CONCLUSIONS

This study has assessed 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 virological 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/HCV infection 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 the mean 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.
HIGHLIGHTS

- Patients with cancer should receive a screening for viral hepatitis before starting systemic anticancer therapies, including immunotherapy.

- An antiviral prophylactic therapy should be evaluated in patients with chronic HBV infection receiving systemic anticancer treatment.

- The management of immune checkpoint inhibitors (ICIs) in patients with cancer and concurrent HBV/HCV infection requires a multidisciplinary approach.

- The enrollment of patients with HBV/HCV infection in oncology clinical trials with ICIs should be improved.
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Marco Tagliamento: Travel, Accommodations, Expenses: Roche, Bristol-Myers Squibb, AstraZeneca, Takeda, Eli Lilly. Honoraria as medical writer: Novartis, Amgen, MSD. None related to the current manuscript.

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REFERENCES


Table 1. Characteristics of the practicing centers of surveyed oncologists.

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<tr>
<th>Country</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Italy</td>
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<td>France</td>
<td>15 (27%)</td>
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<td>Spain</td>
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<table>
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<th>Number of patients already treated with ICI</th>
<th>N (%)</th>
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<tr>
<td>&lt; 50</td>
<td>15 (27%)</td>
</tr>
<tr>
<td>51 – 100</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>101 – 150</td>
<td>7 (12%)</td>
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<tr>
<td>&gt; 150</td>
<td>24 (43%)</td>
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<th>Estimated distribution of patients treated with ICI by cancer type</th>
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<tr>
<td>Lung</td>
<td>35%</td>
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<td>Melanoma</td>
<td>21%</td>
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<tr>
<td>Renal cell carcinoma</td>
<td>15%</td>
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<tr>
<td>Head and neck</td>
<td>11%</td>
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<tr>
<td>Urothelial cancer</td>
<td>9%</td>
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<tr>
<td>Hepatocellular carcinoma</td>
<td>5%</td>
</tr>
<tr>
<td>Others</td>
<td>4%</td>
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**Abbreviations.** ICI: immune checkpoint inhibitors
FIGURES’ TITLES AND LEGENDS

Figure 1
Title: Perception on immunotherapy administration to patients with active viral hepatitis
Caption: Are you usually afraid of treating with ICIs patients with solid tumor and active HBV/HCV infection? (active HBV infection = positive HBsAg or detectable HBV-DNA, negative anti-HBs; active HCV infection = detectable HCV-RNA)

Figure 2
Title: Screening for HBV/HCV infection
Caption: Do you usually test for HBV and HCV status before starting a treatment with ICIs?

Figure 3
Title: Management of viral infection in patients with cancer treated with immunotherapy
Caption: How do you usually manage patients with active HBV or HCV infection treated with ICI?
Yes, so I usually don’t treat them
Yes, but it happened to treat selected cases
No
Yes, routinely: 63%
No: 21%
Sometimes: 16%
- Start ICI monitoring only transaminases
- Start ICI monitoring transaminases and HBV-DNA or HCV-RNA periodically
- Start ICI dosing HBV-DNA or HCV-RNA if there is a hepatitis flare
- Antivirals administration before and during ICI
AUTHORS’ CONTRIBUTION
Marco Tagliamento: conceptualization, methodology, data curation, project administration, writing (original draft, review & editing).
Jordi Remon: project administration, writing (original draft, review & editing).
Matteo Giaj Levra: project administration, writing (review & editing).
Andrea De Maria: methodology, writing (review & editing).
Paolo Bironzo: conceptualization, methodology, writing (original draft, review & editing).
Benjamin Besse: supervision, writing (review & editing).
Silvia Novello: supervision, writing (review & editing).
Laura Mezquita: conceptualization, supervision, writing (original draft, review & editing).