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Immuno-Oncology

Immunotherapy in Underrepresented Populations of Patients with Cancer: Do We Have Enough Evidence at Present? A Focus on Patients with Major Viral Infections and Autoimmune Disorders

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Key Words. Cancer • Immune checkpoint inhibitors • Infections • Rheumatic diseases • Autoimmune diseases

Abstract

The safety and activity of immune checkpoint inhibitors have been characterized in interventional and observational studies. However, only small studies have specifically investigated these agents in patients who are excluded or underrepresented in clinical trials, frequently referred to as "special populations" or "underrepresented populations." These include older adults, those with dysregulated immune activation, patients with a compromised immune function, and those carrying major viral infections, lymphoproliferative diseases, and major organ dysfunctions. Therefore, there remains substantial uncertainty regarding the use of immune checkpoint inhibitors in these specific settings. The Network of Italian Supportive Care in Oncology has carried out a multidisciplinary project, with the contribution of oncologists and other specialists, to retrieve the existing evidence on the use of immunotherapy in patients with solid and hematological cancers with the final aim to provide an expert guidance. The results of this effort are presented in this article, which is focused on patients with major viral infections or those with immune dysregulation/autoimmune diseases, and could be useful to guide decisions in clinical practice and to design prospective clinical trials focusing on the use of immunotherapy in these populations. ***The Oncologist*** 2020;25:e946–e954

Implications for Practice: Substantial uncertainty remains regarding the use of immune checkpoint inhibitors in "underrepresented" patients, such as older adults, those with dysregulated immune activation, and patients with a compromised

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immune function, major viral infections, lymphoproliferative diseases or major organ dysfunctions. The Network of Italian Supportive Care in Oncology has carried out a multidisciplinary project to retrieve the existing evidence on the use of immunotherapy in underrepresented patients with cancer in order provide an expert guidance. The results of this effort, with a focus on patients with major viral infections or those with immune dysregulation/autoimmune diseases, are presented in this article and could be useful to guide decisions both in clinical practice and to design clinical trials.

Introduction

Immunotherapy has represented an unprecedented advance of the therapeutic landscape in oncology. Many drugs are now approved in the treatment of different tumors, including melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma, urothelial cancer, head and neck squamous cell carcinoma, and Merkel cell carcinoma, and a list of other approvals is foreseen in the near future. Indeed, immune checkpoint inhibitors (ICIs) have demonstrated broad activity, with response rates ranging from 15% to 90% in more than 10 different cancer types [1, 2]. Moreover, these agents frequently induce durable disease control, although definitive cure is achieved only in a minority of patients. Their safety is generally considered favorable compared with historical chemotherapy regimen, although a small, but not negligible, incidence of treatment-related severe adverse events (AEs) has been recently reported in a large meta-analysis with some differences in tolerability profiles among different agents [3]. These toxicities, in particular immune-related AEs (irAEs), are generating a new area of knowledge and networking among medical physicians. Despite this, many studies have tried to define the predictive role of PD-L1 expression and other biomarkers, including tumor mutational burden. Identifying reliable predictive biomarkers of efficacy and toxicity of ICIs does represent a major unmet need in clinical practice [4].

The safety and activity of ICIs have been well characterized in numerous clinical trials. However, to our knowledge, only small studies have begun to explore the safety of these agents in patients who are excluded or underrepresented in clinical trials (frequently called "special populations"), including older adults, those with dysregulated immune activation (preexisting autoimmune diseases or immunosuppression due to hematopoietic/solid organ transplant receipt), patients with a compromised immune function (long-term immunosuppression), or those carrying major viral infections, lymphoproliferative diseases and major organ dysfunctions, or other comorbidities (e.g., diabetes). Despite these early efforts, there remains substantial uncertainty regarding the use of ICIs in these special settings.

Of note, the use of immunotherapy in underrepresented populations of patients with cancer has seldom been reviewed systematically [4], although several reviews have investigated the use of these agents in specific subpopulations (e.g., elderly patients, transplant recipients, or those with lymphoproliferative disorders) [5–11].

Therefore, the Network of Italian Supportive Care in Oncology (NICSO) has carried on a multidisciplinary project, with the contribution of oncologists and other specialists, to retrieve and discuss the existing evidence on the use of immunotherapy in patients with cancer and concomitant major viral infection or immune dysregulation/autoimmune diseases. The results of this effort are presented in this article and could be useful to guide decisions in clinical practice and to design prospective clinical trials focusing on the use of immunotherapy in these populations.

Definition of Underrepresented Populations

All underrepresented populations were defined as follows: (a) elderly patients (considered as >65 years or >70 years, according to the different classifications in the studies), (b) patients with underlying major infections (hepatitis B virus [HBV], hepatitis C virus [HCV], or human immunodeficiency virus [HIV]), (c) patients with preexisting autoimmune diseases of any kind, (d) solid transplant recipients, or (e) patients with lymphoproliferative disease or receiving transplant for hematological malignancy. Given the extensive number of excellent reviews on the use of immunotherapy in elderly patients or in transplant recipients [5–11], we decided to focus on patients with major viral infections and autoimmune diseases in the present article.

Because of their peculiar characteristics, pediatric patients were not considered for the present project.

The Project

NICSO is a nationwide, Italian network funded for the promotion of knowledge, clinical practice, and research in the field of supportive care in cancer. The network received scientific recognition by the Multinational Association of Supportive Care in Cancer in 2014.

NICSO decided to carry out a project, which aimed to collect existing evidence on the use of immunotherapy in underrepresented populations of patients with cancer. To this end, a Steering Committee was appointed (P.B., A.A., and F.R.). The Committee gathered consent to participation of other Italian colleagues with different backgrounds (oncologists, hematologists, transplant specialists, geriatricians, gastroenterologists, dermatologists, rheumatologists, infectious disease specialists). The assistance of an independent scientific consultancy agency (Polistudium srl, Milan, Italy) was also sought in order to guarantee scientific accuracy, facilitation of meetings, and preparation of materials. The entire project was supported by an unrestricted and unconditional grant from Merck Sharp & Dohme, which was not offered the opportunity to see or revise the output of the meetings or of any other material and had no role in the submission process.

The participants attended three meetings from October 2018 to May 2019. During the first meeting, the Steering Committee discussed the aims of the project with the other participants. Then, a comprehensive literature research on the use of immunotherapy in the abovementioned populations was conducted using MEDLINE with different combinations of pertinent keywords (e.g., cancer AND

immunotherapy AND elderly AND [anti-PD-1 OR anti-PD-L1 OR anti-CTLA-4 OR immune checkpoint inhibitors]; cancer AND immunotherapy AND infection AND [HBV OR HCV OR HIV] AND [anti-PD-1 OR anti-PD-L1 OR anti-CTLA-4 OR immune checkpoint inhibitors]). Full-text articles were collected and saved in a dedicated online repository available to all participants. During the second meeting, the results of the literature research were freely discussed among all participants. Thereafter, two participants (an oncologist and another specialist with relevant background in each topic) were asked to (a) select the most relevant articles for each of the abovementioned populations, using Critical Appraisal Skills Programme checklists as a guide [12]; (b) identify further references from their personal collection of literature or other sources, including major scientific congresses; and (c) provide their personal opinion, based on evidence review and clinical experience on the topic. The participants presented the results of their work during the third meeting using a predefined template. All participants then freely discussed each presentation; the outcomes of the discussion represent the basis for the present article.

Safety Considerations

In terms of safety we reported literature data on both treatment-related AEs and irAEs. Treatment-related AEs are defined as any new event or worsening in intensity of frequency of previous events after exposure to treatment, whereas irAE refers to specific side effects associated with the increased activity of the immune system by ICIs. irAEs may affect multiple organs, including skin, gastrointestinal tract, endocrine system, liver, lung, nervous systems, and musculoskeletal systems [13].

Patients with Major Viral Infections

With some exceptions, HBV, HCV, and HIV infections represent a near-universal exclusion criteria in trials of immune checkpoint inhibitors in the oncological setting. Indeed, these infections contribute to suppress T-cell function and, at least in theory, may compromise the efficacy of these agents, particularly in patients with low $CD4^+$ T-cell counts caused by HIV infection [4].

Very scant experience with ICIs in patients with cancer and concomitant HBV and/or HCV infection is available. In a multicenter, retrospective study, 46 patients from 16 centers worldwide (median age, 60 years; 72% with melanoma), of whom 40 presented major viral infections, were analyzed [14]. Four responses were reported in the 12 patients with HIV infection, three responses were reported in the 14 patients with HBV infection, and three in the 14 patients infected by HCV; no unexpected toxicities were reported. Some other anecdotal experiences of successful ICI treatment in patients with cancer and concomitant HIV infection have been also reported [15, 16].

We identified one pilot clinical trial [17] conducted on tremelimumab, an anti-CTLA-4 agent, in addition to ablation, in 32 patients with HCC; 19 of these patients had HCV infection, and 5 had HBV infection [17]. No dose-limiting toxicities were encountered, and the most common toxicity was pruritus (four cases: three of grade 2 and one grade 3). Of the 19 evaluable patients, five (26.3%; 95% confidence interval [CI], 9.1–51.2%) achieved partial response; 6- and 12-month progression-free survival were 57.1% and 33.1%, respectively, with a median time to progression of 7.4 months and a median overall survival of 12.3 months. In total, 12 of 14 patients with quantifiable HCV showed a marked reduction in viral load, and tumor biopsies showed a clear increase in $CD8^+$ T cells for patients reporting clinical benefit. Moreover, the KEYNOTE-224 trial investigated the efficacy and safety of pembrolizumab in 104 patients with HCC previously treated with sorafenib, including patients affected by HCV (n = 26) or HBV (n = 22). Overall, the study showed that pembrolizumab was effective and tolerable in this population. No difference in objective response was detected in the subgroup analysis of patients with major infections: a reduction in tumor target lesion size was detected in 57% of patients with HBV, 39% of patients with HCV, and 58% of those without major infections. Treatment was overall tolerable, and no cases of flares of HBV/HCV were reported [18].

Overall, treatment for HCV should be considered for all patients with detectable viral load because highly effective and safe drugs are now available for this infection. However, the panelists believe that with the clinical need of promptly starting cancer treatment, immunotherapy may also be offered with untreated HCV.

With respect to HBV, patients with active HBV infection (hepatitis B surface antigen [HBsAg] positive, HBV DNA ≥2,000 IU/mL, alanine aminotransferase [ALT] above the upper limit of normal) should be put on long-term therapy with entecavir or tenofovir until HBsAg seroconversion. Inactive carriers of HBsAg (HBsAg positive, hepatitis B e-antibody positive, HBV DNA <2,000 IU/mL, ALT normal) on ICIs should receive prophylaxis with lamivudine, entecavir, or tenofovir until 12–18 months after completion of ICI treatment, although risk of reactivation is probably low. Last, patients with cured HBV infection (HBsAg negative, hepatitis B surface antibody positive, hepatitis B surface antibody positive or negative) should be monitored for HBsAg or HBV DNA and liver function without active therapy [19, 20].

All patients carrying the HIV infection should start antiretroviral therapy. A few cases of patients with cancer and HIV infection treated with ICIs have been reported [21–24].

In a recent publication, 73 patients with HIV and cancer treated with ICIs have been reviewed; 69 (94.5%) were receiving antiretroviral therapy; ICIs were generally well tolerated, with grade 3 or higher treatment-related AEs noted in 8.6% of cases, and response rates were generally comparable to those reported for the general population; HIV viral load generally remained suppressed and CD4 count slightly increased [25]. Consistently, preclinical data suggest that ICIs may reduce viral load and increase the CD4 count in HIV infection because of their ability to reverse T-cell exhaustion [25]. Furthermore, limited data suggest that ICIs may play a role in depleting reservoirs of HIV [26]. Quantification of HIV viral load and CD4 count should be performed before the initiation of immunotherapy and periodically thereafter. Patients with HIV infection have a theoretical risk of immune reconstitution inflammatory syndrome while on ICI therapy, but the current evidence suggests that it is very unlikely [25]. A phase I study on pembrolizumab in 30 patients with cancer

and concomitant HIV infection and on antiretroviral therapy was recently published [27]. Safety was observed over a total of 183 cycles of therapy. Most treatment-emergent AEs potentially related to pembrolizumab were mild, with only 20% of patients experiencing grade 3 events. The most common AEs were hypothyroidism (n = 6), followed by pneumonitis (n = 3). One patient died of an AE (Castleman disease). Increasing CD4 counts were observed during therapy. One case of complete response was observed (lung cancer) and two partials responses (non-Hodgkin lymphoma) were observed. On these bases, the authors of the study suggested that patients with HIV meeting appropriate eligibility criteria should not be denied the opportunity to enter clinical trials on immunotherapy.

Expert Opinion

Overall, treatment with ICIs appears to be safe in patients with properly managed HCV, HBV, or HIV infection, in line with previous suggestions [25, 28, 29]. Moreover, considering the current data available, in terms of objective response there are no significant differences with disease population who do not carry any major infection. Complete screening for HBV, HCV, and HIV, followed by determination of viral load, should be performed before the initiation of oncological treatment, and patients should be referred to an infectious diseases specialist for assessment. A subsequent follow-up made together with the specialist is mandatory after completion of ICI therapy to discover the potential late viral reactivation of the underlying diseases early. In future studies, timing of starting antivirals and ICIs in treatment-naive patients with HBV, HIV, or HCV infection, and a possible role of ICIs in patients with HIV infection without cancer should be investigated.

Patients with Immune-Mediated Disease

Dysregulated immunity underlies several autoimmune disorders, including inflammatory bowel disease, autoimmune hepatitis, Guillain-Barré syndrome, psoriasis, and others. The hallmark toxicities of ICIs are due to aberrant activation of autoreactive T cells against host tissues, thus closely mirroring several autoimmune diseases [4, 30–36]. Although most adverse events occurring at the immune system can be resolved with corticosteroid administration, monitoring, and/or hormone replacement, fulminant events may occur, potentially leading to severe morbidity or even mortality.

In particular, the dermatological, endocrine, and gastrointestinal systems are more frequently affected by irAEs. Therefore, it is of interest to analyze the efficacy and safety of ICIs in patients presenting with autoimmune disorders targeting those systems; however, reports of rheumatic irAEs have been sparse and have only been described in case reports or small series. The presence of subclinical autoimmune diseases, indicated by a positive titer of autoantibodies, could represent a predictive marker of development of irAEs, as well as of clinical benefit.

This smoldering autoimmune condition was explored by Toi et al., who demonstrated in a retrospective study that the patients with advanced NSCLC having specific autoimmune markers (i.e., thyroid peroxidase factors, antibody anti-thyroglobulin, thyroid peroxidase, among others) with or without evidence of autoimmune diseases benefit more in term of clinical outcomes when treated with ICIs even if the rate of irAEs is more pronounced in the population with subclinical autoimmune diseases [37]. Remarkably, according to the results of a large (n = 4,438) study on ICI-treated patients, which included an insurance database, 283 of whom had autoimmune disease by relaxed criteria, autoimmune disease was not associated with all-cause hospitalization (hazard ratio [HR], 1.11; 95% CI, 0.91–1.34), although it was associated with hospitalization with an irAE diagnosis (HR, 1.46; 95% CI, 1.06–2.01) and corticosteroid treatment (HR, 1.46; 95% CI, 1.13–1.88) [38].

We comment here on the results of some observational series and case reports of immunotherapy in patients already bearing autoimmune diseases (Table 1).

Weinstock et al. analyzed a total of 552 patients with a documented history of autoimmune disease not dependent on corticosteroids, enrolled in 22 clinical trials of PD-1/PD-L1 immunotherapy agents [39]. The most common autoimmune diseases were thyroid disorder (n = 188), psoriasis (n = 70), and vitiligo (n = 44). Overall, no relevant safety signals were reported, and no worsening of baseline autoimmune disease was identified.

In a prospective study of the French REISAMIC registry, 45 patients with autoimmune disease and receiving anti-PD-1/PD-L1 agents were identified [40]. In total, 20 patients (44.4%) presented with irAEs, associated with a preexisting autoimmune disease ("autoimmune disease flare") in 11 cases. Treatment with ICIs was maintained in 15 out of 20 patients. Remarkably, irAE-free survival time was shorter in autoimmune disease patients than in AIDS-free patients (5.4 vs. 13.0 months), whereas the two groups did not differ in terms of overall survival or objective response rate, thus suggesting that anti-PD-1 antibodies are as effective in patients with autoimmune diseases as in the general population.

In a retrospective study, Johnson et al. evaluated ipilimumab therapy in 30 patients with advanced melanoma and preexisting autoimmune disorders [41]. In total, eight patients (27%) showed exacerbations of their autoimmune condition, all managed with corticosteroids. Grade 3–5 irAEs were reported in 10 patients (33%) and successfully managed by corticosteroids or infliximab in two patients. In another small (n = 16) retrospective analysis performed at the Mayo Clinic, irAEs occurred in six patients, with no differences in time from cancer diagnosis to immunotherapy, duration of immunotherapy, age, or sex between the patients with and without irAEs [42].

A larger (n = 119; 52 with preexisting autoimmune diseases and 67 with prior irAEs) study on ipilimumab in patients with melanoma reached similar conclusions, with 38% of patients with autoimmune disease experiencing a flare of disease requiring immunosuppression. Interestingly, none of those patients presented gastrointestinal or neurological autoimmune disorders, and only two patients discontinued the treatment [43]. Among patients with previous irAEs, 2 (3%) patients had a recurrence of the same event, 23 (34%) developed new irAEs (14, 21% grade 3–4), and 8 (12%) discontinued therapy. In a retrospective study on 56 patients with NSCLC with autoimmune disease treated with

Table 1. Key studies on patients with cancer and autoimmune disease

Study	Design	Patients	Key findings
Kehl et al. [38]	Retrospective study	283 with autoimmune disease (by relaxed criteria) treated with ICIs	No association between autoimmune disease and all-cause hospitalization Modest increase in hospitalization in patients with irAE (HR 1.46) and corticosteroid treatment (HR 1.46)
Richter et al. 2018 [42]	Retrospective study	16 with history of autoimmune diseases	Incidence of irAEs: 37.5% No difference in time from cancer diagnosis to immunotherapy, duration of immunotherapy, age, or sex between patients with or without irAEs
Weinstock et al. [39]	Pooled analysis of 22 trials on anti-PD-1/PDL-1	552 with history of autoimmune disease	No relevant safety signals No worsening of autoimmune disease
Danlos et al. [40]	Prospective registry study	45 patients with autoimmune disease and on anti-PD-1/PD-L1	Incidence of irAE: 44.4% irAE-free survival time shorter in patients with AIDS than in autoimmune disorder–free patients (5.4 vs. 13.0 months) No differences in survival or response
Johnson et al. [41]	Retrospective study	30 patients with advanced melanoma and autoimmune disease treated with ipilimumab	Incidence of autoimmune disorder exacerbation: 27% Grade 3–5 irAEs reported in 10 patients (33%)
Menzies et al. [43]	Retrospective study	119 patients with melanoma (52 with prior autoimmune disease and 67 with prior irAE) treated with ipilimumab	38% of patients with autoimmune disease experienced a flare; only two discontinued treatment Among patients with previous irAE, 2 (3%) patients had a recurrence of the same event; 23 (34%) developed new irAEs, and 8 (12%) discontinued therapy
Leonardi et al. [44]	Retrospective study	56 patients with NSCLC and autoimmune disease treated with different anti-PD-1/PD-L1 agents	Incidence of flare: 23% Incidence of irAE: 38%
De Bock et al. [45]	Case series	35 patients with psoriasis as irAE during anti-PD-1/PD-L1 treatment	Treatment suspension in 26% (n = 9)
Cortellini et al. [51]	Prospective study	751 patients with advanced cancer treated with anti-PD-1/PD-L1; 11.3% with preexisting autoimmune disease	Incidence of irAEs higher in those with autoimmune disorders (66% vs. 40%) No differences in incidence of grade 3–4 events or efficacy
Le Burel [52]	Retrospective study	908 with systemic autoimmune, inflammatory, and/or rheumatic diseases or immune cytopenia treated with anti-PD-1/PD-L1 agents	Higher incidence of irAEs in patients treated with two ICIs: from 1% to 2.5% Mostly moderately severe irAEs (63% grade 2) Almost all irAEs fully or partially resolved (93%)
Tagliamento et al. [48]	Case report	Patient with advanced non-small-cell lung cancer, lupus erythematosus, and HCV infection treated with nivolumab	Successful response
Puri et al. [49]	Case report	78-year-old man with melanoma and rheumatoid arthritis treated with pembrolizumab	CR after 4 months No worsening symptoms or laboratory parameters of the autoimmune disease
Linge et al. [50]	Case report	60-year-old man with Merkel cell carcinoma, HIV infection, and pulmonary sarcoidosis treated with pembrolizumab and avelumab	CR after 1 year of treatment with avelumab

(continued)

Table 1. (continued)

Study	Design	Patients	Key findings
Jordan et al. [47]	Case report	49-year-old woman with recurrent CNS lymphoma and MG treated with nivolumab	No clinical evidence of MG or lymphoma after 36 months of treatment No irAEs (except MG)
Gutzmer et al. [58]	Retrospective study	41 with MM and preexisting autoimmunity (*n* = 19, group A) or previous ipilimumab-triggered irAEs (*n* = 22, group B) treated with PD-1 inhibitors	Incidence of flare: 42% vs. 4.5% Incidence of new irAEs: 16% vs. 23% No discontinuations Tumor response rate above 30% and unrelated to irAEs
Zaremba et al. [54]	Case report	61-year-old woman with advanced MCC and history of MG treated with pembrolizumab	Long-lasting tumor response (up to 65 weeks) with partial remission of metastases No flare of MG
Lidar et al. [55]	Retrospective study	400 patients with cancer treated with ipilimumab, pembrolizumab, and/or nivolumab	Rheumatic irAE: 3.5% The most common irAE was inflammatory arthritis (85%) Rheumatic manifestations tend to occur later compared with other irAEs

Abbreviations: CNS, central nervous system; CR, complete response; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MCC, Merkel cell carcinoma; MG, myasthenia gravis; MM, metastatic melanoma; NSCLC, non-small-cell lung cancer.

different anti-PD-1/PD-L1 agents, exacerbation of the preexisting autoimmune disease was reported in 23% of cases, and irAEs were reported in 38% (grade 1–2 in three-quarters of cases) [44].

Immunotherapy was permanently discontinued in eight patients (14%) because of irAEs. In a recent review of 35 reported cases of psoriasis as irAEs in patients undergoing treatment with anti-PD-1/PD-L1 checkpoint inhibitors, temporary suspension of treatment was necessary in nine cases, and psoriasis was managed according to the current guidelines [45]. One report documented the case of a patient with advanced melanoma and refractory Crohn's disease who received concomitant pembrolizumab and tocilizumab [46]. The treatment was well tolerated and did not result in exacerbations of Crohn's disease. Last, recent case reports documented successful use of nivolumab in a patient with myasthenia gravis in remission [47], of the same drug in a patient with lung cancer and concomitant lupus erythematosus plus HCV infection [48], of pembrolizumab in a patient with melanoma and rheumatoid arthritis [49], and of avelumab in a patient with Merkel cell carcinoma, HIV infection, and sarcoidosis [50].

Very recently, Cortellini et al. evaluated 751 consecutive Italian patients with advanced cancer (median age: 69 years; most frequent cancer types, NSCLC, 65.5%, and melanoma, 21.2%) treated with anti-PD-1 agents [51]. In total, 85 patients (11.3%) had preexisting autoimmune disease (active in 17.6% of cases). Incidence of any-grade irAEs was significantly higher in patients with autoimmune disease than in those without (65.9% vs. 39.9%). Both inactive and active preexisting autoimmune disease, female gender, and Eastern Cooperative Oncology Group performance status <2 were associated with a higher incidence of irAEs. No differences were observed between patients with autoimmune disease and those without regarding grade 3/4 irAEs and objective response rate or survival.

Overall, available real-life data, although reported in small populations and often in retrospective studies, have shown that ICIs can induce a wide variety of rheumatic irAEs and, in particular, inflammatory arthritis [51–55].

Expert Opinion

The frequency of rheumatic irAEs in patients already affected by rheumatic diseases who develop cancer is higher. Patients may experience exacerbations of their autoimmune condition necessitating systemic treatment. In this case, rheumatic irAEs are often mild and can usually be managed with steroids or immunosuppressive therapy [56, 57]. However, rarely, immune reactions can be fatal. This must be considered and carefully evaluated before starting immune checkpoint inhibitor treatment and during ICI treatment, also given that patients with rheumatologic disorders show increased risk of reactivation of underlying disease or prolongation of flares with ICI, requiring assessment of disease status before starting treatment and during ICI therapy. Adequate subsequent follow-up is mandatory after immunotherapy completion [39, 40, 58–63].

Overall, active or prior autoimmune disease controlled by appropriate therapies should not represent an absolute contraindication of ICI use because irAEs flares are usually well manageable with supportive care and multidisciplinary follow-up without definitive interruption of ICI treatment [52]. Recent data, even if case reports or series, also showed feasibility of ICIs in preexisting and multiple autoimmune diseases independently of their status (active or not).

Overall, immunotherapy with ICIs is as effective in patients with autoimmune diseases as in the general population.

Strengths and Limitations

This study provides a broad picture of literature evidence on the safety and efficacy of ICIs in underrepresented

Table 2. Summary of the main practical suggestions for ICI treatment in oncological patients with major viral infection and autoimmune diseases

Condition	Additional examinations or treatment required	Safety profile of ICIs	Overall guidance
Major viral infection			
HIV infection	Start antiretroviral therapy before ICIs Perform quantification of viral load and CD4 count before, during, after ICIs	Generally well tolerated Mild AEs detected, such as hypothyroidism and pneumonitis Theoretical risk of IRIS (very unlikely)	Treatment with ICIs should be considered in patients with properly managed infection Perform a complete screening for HCV, HBV, and HIV with determination of the viral load before ICI start Refer the patient to an infectious disease specialist before treatment After treatment carefully monitor the patient for potential viral reactivation
HBV infection	Long-term treatment with entecavir or tenofovir in case of active infection until HBsAg seroconversion Prophylactic treatment with lamivudine, entecavir or tenofovir for inactive carriers, up to 12–18 months after ICIs completion Long-term monitoring for HBsAg/HBV DNA and liver function during and after ICIs treatment	No dose-limiting toxicity Most common toxicity: pruritus	
HCV infection	Appropriate HCV treatment for patients with detectable viral load before ICIs Untreated patients may also start ICIs		
Autoimmune disease			
Rheumatic diseases	Steroids or immunosuppressive therapy in case of irAEs or disease flare	Higher risk of rheumatic irAEs Risk of disease reactivation/ prolongation of flare	Careful assessment of disease status before ICIs Careful monitoring during and after therapy

Abbreviations: AE, adverse event; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IRIS, immune reconstitution inflammatory syndrome.

populations, summarizing the main recommendation available in literature and providing the opinion of a multidisciplinary group of Italian experts to guide clinical practice (Table 2). We acknowledge that the observations provided in the study are limited by the scant availability of large trials and systematic review on this topic, and we therefore advise that future clinical trials should be carried out on the use of ICIs in these peculiar populations. The opinions expressed in this article could also be useful in defining the best design and focus of these future trials.

Conclusion

The use of ICIs in the treatment of human cancers is rapidly evolving. The characterization of their efficacy and safety in real-world patient populations, usually not included in clinical trials, is a critical objective of the medical community in view of the upcoming approval of these agents in many different cancers and populations.

A comprehensive review of the available literature on patients with concomitant major viral infection or autoimmune disorders of any kind has shown that these agents usually have acceptable safety profiles even in these underrepresented populations. It would be obviously helpful to perform prospective studies in these populations in order to extend and validate the results reported so far, even if completing such trials would be difficult. Another goal to be pursued is the identification of reliable predictive biomarkers of efficacy and toxicity in these populations at higher risk of adverse events. Meanwhile, clinicians should consider the available data when making treatment decisions in patients with concomitant major viral infection or autoimmune disorders of any kind, balance the risks of toxicity with potential benefits, and make such decisions in a multidisciplinary setting [64].

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Disclosures

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