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Multidisciplinary management of cancer patients with immune-related adverse events from checkpoint inhibitors

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Multidisciplinary management of cancer patients with immune-related adverse events from checkpoint inhibitors

Topic editors

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Editorial: Multidisciplinary management of cancer patients with immune-related adverse events from checkpoint inhibitors

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Editorial on the Research Topic
Multidisciplinary management of cancer patients with immune-related adverse events from checkpoint inhibitors

Cancer immunotherapy with immune checkpoint inhibitors (ICI) has revolutionized the management of many frequent advanced tumors, such as lung cancer (1). These therapies have markedly improved the survival of cancer patients decreasing the rates of recurrence and progression of the underlying malignancies (2, 3). However, the widespread use of ICIs has also lead to an exponential rise of immune-related adverse events (irAEs) associated with these drugs.

As summarized in Figure 1, real-world practice has brought to light substantial challenges in many aspects of the management of irAEs, for instance in the diversity of clinical manifestations, the grading of severity and strategies for treatment, with concerns about the potential effect of immunosuppressants on the efficacy of ICIs. Furthermore, immunotherapy is now used in special cancer populations such as those infected by human immunodeficiency virus (HIV), patients who have received solid-organ transplantation, individuals with underlying autoimmune disorders, or patients with latent infections such as tuberculosis o viral hepatitis, who can develop reactivation of their infections when they receive therapy with ICIs. Altogether, these issues highlight the vital importance of collaborative teamwork in order to optimize the prognosis of patients who develop irAEs or other complications as a consequence of receiving ICI. These challenges are the theme of this Research Topic of *Frontiers in Medicine* entitled

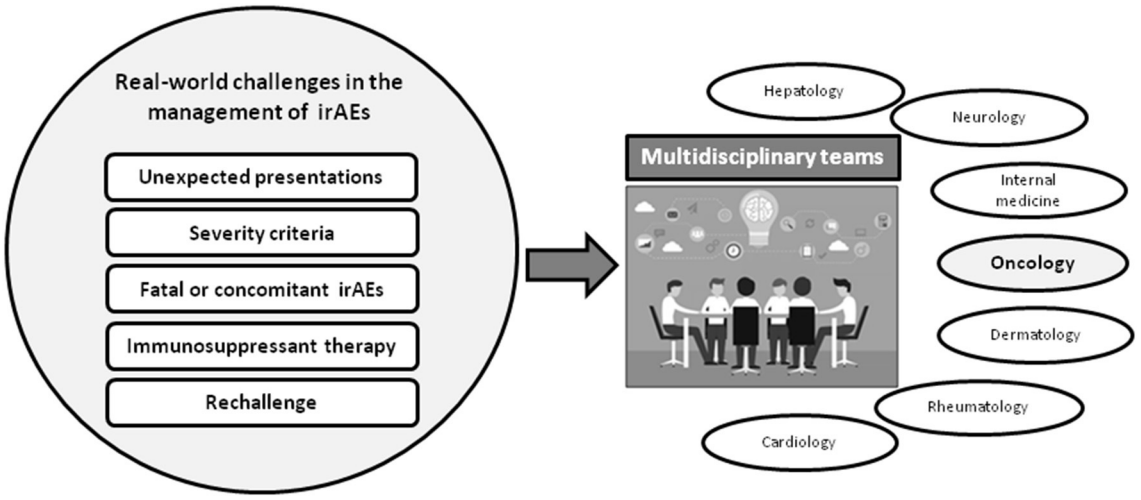

FIGURE 1
Pitfalls of real-world practice immune-related adverse events associated with immune checkpoint inhibitors (ICIs) and need of multidisciplinary teams for their management. The difficulties and differences between irAEs reported at the clinical trials and real-world practice highlight the importance of the multidisciplinary management of patients with severe irAEs.

"*Multidisciplinary Management of Cancer Patients with Immune-Related Adverse Events from Checkpoint Inhibitors.*"

Immunotherapy in special populations

It is well-known that patients who have received solid-organ transplantation are at increased risk of subsequent cancer, and may be eligible to receive ICI. On this topic, Bermejo et al. summarize the outcomes and controversies surrounding the treatment with ICIs in patients with prior kidney transplantation. One of the hot topics in this field is the risk of acute rejection associated with ICI therapy. Concomitant treatment with mTOR monotherapy, low-dose corticosteroids or even a "dynamic immunosuppression" scheme seems to reduce the incidence of rejection. The efficacy of this last approach will be assessed in a prospective cohort, and robust results may be available soon (Bermejo et al.).

The increased survival of patients with HIV, currently comparable to those non-infected, highlights the need to provide access to effective therapeutic cancer therapies in this population, as shown in the paper by Aguilar-Company et al. In this setting, incidence of irAEs seems similar to that observed in the general cancer population, without changes in plasma viral loads (Aguilar-Company et al.).

The coexistence of an autoimmune disorder with cancer is of special relevance for therapy with ICIs, as there are risks of flares of the pre-existing autoimmune disease, as well as a potential for higher incidence of irAEs (Aguilar-Company et al.). As learnt from studies of patients with inflammatory bowel disease or rheumatoid arthritis, patients with good control of their autoimmune disorder prior to beginning ICI therapy are less likely to develop exacerbations during immunotherapy (4) (Aguilar-Company et al.). Fortunately, concomitant treatment with immunosuppressive drugs, including anti-TNF agents, seems safe in patients receiving ICIs (Robles-Alonso et al.).

Immune checkpoint inhibitors and risk of latent infections

Widespread use of ICI has highlighted the risk of reactivation of latent infections such as tuberculosis or viral hepatitis with these agents.

In registry studies all patients with hepatitis B and C had to be virologically suppressed, with the exception of those with hepatocellular carcinoma. Although, ICIs have no impact on hepatitis C virus (HCV) and could even decrease HCV-RNA, screening for HCV is highly recommended in cancer patients to assess potential concomitant cirrhosis and further risk of decompensation (5). Concerning hepatitis B, patients with chronic hepatitis B, that is those with positive HBsAg, are at risk of reactivation when receiving ICIs (6), so they can benefit from concomitant antiviral prophylaxis, as is recommended for those undergoing chemotherapy (5). Hitherto, data on the risk of hepatitis B reactivation on patients with resolved infection i.e., testing negative for HBsAg but positive for anti-HBc, is scarce. In this Research Topic, Aceituno et al. reported the absence of hepatitis B reactivation in a cohort of 75 subjects with resolved HBV infection. Interestingly, authors also reported the relatively low awareness of oncologists about the risk of viral hepatitis

reactivation in patients on ICIs, with only 55% of subjects having the complete serology panel performed before immunotherapy was started (Aceituno et al.).

There is a need for further studies regarding the risk-benefit and the proper strategy for management of latent tuberculosis in individuals about to initiate ICIs. Current evidence does not clearly support routine latent tuberculosis infection screening, and treatment for latent tuberculosis should be weighed on an individual basis, accounting for potential pharmacological interactions, risk of hepatotoxicity and expected survival (Aguilar-Company et al.).

Treatment of severe immune-related adverse events

One of the hottest topics on the management of irAEs is the treatment of severe grade-3 and grade-4 adverse events. Corticosteroids have been the backbone of therapy of severe irAEs in both registry studies and international guidelines (7, 8). However, real-world practice has revealed that for many patients with severe irAEs, temporal discontinuation of ICIs may result in improvement without need of immunosuppressant therapy, for instances in immune-mediated hepatitis (9, 10). Moreover, data on some irAEs has shown the potential benefits of early access to corticosteroid-sparing agents. On this regard, studies of real-world clinical practice indicate that specific therapy for irAEs in accordance with the autoimmune disorders they mimic may be beneficial. For example, in the case of immune-related colitis, early access to endoscopy can identify subjects with ulcers or pancolitis who will benefit from infliximab therapy (4). Similarly individuals with severe immune-related arthritis could benefit from early therapy with TNF or IL-6 inhibitors (11).

However, an outstanding issue associated with the use of immunosuppressant drugs is their potential harm on cancer progression, especially taking into account the advanced stage of tumors in the majority of patients undergoing ICIs. As summarized by Bruera et al., the potential deleterious effect of corticosteroids on cancer progression seems to be associated with dose and timing of use. Concomitant treatment with corticosteroids at the initiation of ICIs can negatively impact overall and progression-free survival, whereas temporal or intermittent corticosteroids such as are used often for irAEs, do not seem to negatively impact survival (Bruera et al.).

Rechallenge with immune checkpoint inhibitors after a severe irAE

Once an irAE is resolved, the next step is to assess the possibility of ICI rechallenge. The majority of clinical trials and, in consequence, the international guidelines, recommend against retreatment after a severe irAE. However, a few reports have suggested a strong correlation between the development of irAEs and a better response to ICIs (12); [Cardeña-Gutiérrez and López Barahona]. Moreover, for many patients there are no further alternatives for therapy beyond ICIs. Altogether, these have led to rechallenge with ICIs after recovery from a severe irAE. Real-world data from subjects with history of a severe gastrointestinal irAE have revealed that relapse is not universal, ranging from 24% among patients with prior immune-related colitis to 35% in those with previous immune-related hepatitis (13, 14). Despite this data, retreatment with ICIs after a severe irAE, as many other aspects about immunotherapy, remains a hot topic, with low agreement even among experts on their management (15).

In summary, several challenges remain in the management of severe irAEs which require collaborative multidisciplinary efforts. As clinical trials of ICIs did not include special populations such as those with pre-exiting autoimmune diseases or transplants, or patients with chronic infections, initially there were concerns about treating with ICIs cancer patients with these disorders. As new real-world evidence emerges, it is becoming increasingly clear, that cancer patients with these concomitant comorbidities can also benefit from immunotherapy and should not be denied treatment in most cases. Careful multidisciplinary management with an emphasis in controlling concomitant comorbidities can result in successful therapy in these patients, for many of whom immunotherapy will be their last therapeutic alternative.

Author contributions

Drafting of the manuscript: MR-B. Critical revision of the manuscript for important intellectual content: EF and MS-A. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Overview of Checkpoint Inhibitors Mechanism of Action: Role of Immune-Related Adverse Events and Their Treatment on Progression of Underlying Cancer

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In recent years, immunotherapy-based regimens have been included into the treatment's algorithm of several cancer types. Programmed death-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) interact with their ligands found on the surface of antigen presenting cells (APC) or tumor cells (PD-L1/2 and CD80/86). Through these interactions, stimulatory or inhibitory signals are established. Immune checkpoint inhibitors (ICIs), block these interactions, and when administered not only as monotherapy but also as part of combination regimens, have shown to improve survival results in multiple advanced cancers leading to an increasing number of patients treated with ICI and, as a consequence, a rise in the number of patients developing immune-related adverse events (irAEs). Presence of irAEs has been associated with greater benefit from treatment, especially when blocking PD-L1. Recent data suggests that treatment benefit persists after discontinuation of ICIs due to a treatment related adverse event, regardless of the grade. Patients experiencing grade 3-4 irAEs are at risk of toxicity recurrence after reintroducing immunotherapy and therefore, the decision to resume the treatment is challenging. In these cases, a multidisciplinary approach is always needed and several factors should be considered. Management of severe toxicities may require systemic corticosteroids which can impact on T-cell function. Due to their immunosuppressive properties, it is necessary to deeper determine how corticosteroids influence responses. In terms of overall survival (OS), the use of steroids as therapy for irAEs seems not to reduce OS and several studies have reported durable responses in patients experiencing autoimmune toxicities treated with corticosteroids.

Keywords: immune checkpoint inhibitors (ICIs), immune-related adverse events (irAEs), corticosteroids, efficacy, multidisciplinary management

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INTRODUCTION

Over the last decade, immunotherapy has radically changed cancer therapy.

Since 2011, when Food and Drug Administration (FDA) approved ipilimumab to treat patients with late-stage (metastatic) melanoma (1), several immunotherapies have received regulatory authorities' approval. Different cancer types have shown remarkable responses to this therapy (2, 3). ICIs, as monotherapy but also as part of a combination therapy, improve results in terms of Progression Free Survival (PFS) and Overall Survival (OS) (4–7).

The first tumor types in which immunotherapy was introduced as part of their treatment algorithms were melanoma, Renal Cell Carcinoma (RCC) and Non-Small-Cell Lung Cancer (NSCLC).

Drugs targeting two different checkpoint axis, based on the T-cell membrane (PD-1 and CTLA-4), have shown clinical activity and, indeed, concentrate the biggest evidence in terms of disease control and the largest number of drugs approved and introduced into the clinical practice. Through their interaction with ligands found on the surface of antigen presenting cells (APC) or tumor cells, the immune response is modulated.

Immunotherapy is presented with a specific toxicity profile with diverse types of inflammatory-mediated side effects. The incidence and characteristics of the different adverse events associated with ICIs depend on the patients' profile, cancer diagnosis and type of agent used.

The most common toxicities of ICIs occur at the skin, gastrointestinal mucosa, liver, endocrine glands and respiratory tract (8) but almost every tissue or organ can be affected.

From the pathophysiological point of view, both benefit and toxicity occur as consequence of immune activation. Due to this common etiology, an association between the appearance of irAEs and the benefit of immunotherapy has been proposed (9).

Thus, the development of irAEs has been suggested to be predictive of improved tumor response and better survival in some cancer patients treated with ICIs. However, the occurrence of irAE is not strictly necessary for achieving treatment's benefit (10).

Nowadays, an increasing number of co-stimulatory and co-inhibitory signals participating in the immune response are being identified and targeted. The knowledge about the interactions between them focuses most of the research on this field.

These advances, in terms of disease control and survival, have led to a very significant increase in the number of patients treated with immunotherapy. This large volume of patients receiving immunotherapy has highlighted the need to improve the understanding of the mechanisms of action, the interrelation between the immune signals and the potential toxicity profiles.

Therefore, to improve patient selection it is necessary to consider predictive biomarkers of benefit but also to ensure a correct assessment of their susceptibility to develop irAEs.

MECHANISMS OF ACTION OF ICIS

The immune system protects against tumor growth but also modifies tumor immunogenicity (11). During this process, some tumor cells escape to the antitumor immune response using different mechanisms involving antigens, cytokines and immune checkpoint proteins (12).

Understanding tumor immunology must be achieved through the integration of local immune response in the tumor microenvironment with the changes in the peripheral immune system (13). Immunity in cancer is regulated by diverse cell types in different tissues so its activation or inhibition through cancer immunotherapies may lead to immune responses potentially involving different organs.

Monoclonal antibodies that block the regulatory immune targets CTLA-4, PD-1 and programmed death-1 ligand (PD-L1) are the most well-studied and have the biggest evidence as cancer immunotherapies.

CTLA-4 is present on the surface of CD4-positive and CD8-positive lymphocytes and binds to T-cell–costimulatory factors on the surface of APC. CTLA-4 binding reduces interleukin 2 (IL-2) production and T-cell proliferation.

PD-1 is a receptor expressed on the surface of multiple immune cell types, including T cells, B cells, and NK cells. One of its ligands, PD-L1, is present in different cell types including tumor cells and participates in the inhibition of previously activated T cells.

Approved ICIs include anti-PD1 antibodies (pembrolizumab, nivolumab, cemiplimab), anti-PD-L1 (atezolizumab, avelumab, and durvalumab) and anti–CTLA-4 (ipilimumab, tremelimumab).

In the last few years, a deeper understanding of tumor immunology has led to an increasing number of immunotherapies in clinical development (e.g., blockade of LAG3, TIGIT and TIM3) (14).

The aforementioned pathways can be used by tumor cells to evade the immune system mainly through the inhibition of T-cell function (15).

Checkpoint blockade using ICIs overcomes this tumor-mediated immune inhibition, leading to a proinflammatory tumor microenvironment which potentially increases the disease control but also the risk of triggering an inflammatory-mediated toxicity. ICIs response and toxicity are closely related because of the disinhibition of T-cell3 function. Notably, even in with no history of autoimmune disorders prior to initiation of treatment, irAEs may appear.

T-cells infiltrate is considered to be responsible for both the anti-tumor response and the development of immune-toxicities but, beyond T-cells, a much more complex inflammatory interaction occurs within the immune response.

MECHANISMS OF IRAES

The pathophysiology of irAEs is still under investigation and is not fully understood. Several mechanisms are hypothesized as possible contributors in the development of immune-mediated effects. Autoantibodies, T-cell infiltration, interleukins and other inflammatory cytokines have been proposed to account for the occurrence of irAEs (16).

Regarding autoantibodies, in a study of patients treated with ICIs, the identification of autoantibodies correlated with the development of hypophysitis and pneumonitis (17). Another

study of patients treated with pembrolizumab showed that, up to 80% of patients who developed hypothyroidism had antithyroid antibodies compared with 8% of patients with normal thyroid function (18).

Cytokines levels, at baseline but also after the treatment, have been associated with the development of irAEs (19).

CTLA-4 related adverse events are different from those developed with anti-PD1 therapy since CTLA-4 inhibits T cells in the beginning of the immune response while PD-1 blocks T-cell in peripheral tissues and in a more advanced step of the immune response.

The interaction or relationship between benefit and toxicity, in terms of immune related effects, has been reported in different studies (20, 21) and a deeper knowledge of this interplay will facilitate the identification of risk factors and will help to implement prevention and follow-up strategies.

ASSOCIATION BETWEEN IRAES AND PROGNOSIS IN SOLID TUMORS

Immunotherapeutic agents are widely used in different types of advanced tumors as melanoma, lung cancer, renal clear cell cancer, head and neck cancer and gastrointestinal cancers among others.

There is a subset of patients who benefit most from immunotherapy with long-term survival. The identification of these patients through biomarkers or specific features has been a crucial point for the scientific community in recent past years (22).

In retrospective studies, the presence of irAEs has been associated with clinical benefit. ICIs can induce side effects through the inflammation with lymphocyte infiltration at any organ and consequently a system dysfunction. Most irAEs are mild and transient, nevertheless, sometimes they can be life-threatening. In fact, this can limit retreatment with ICIs after a toxicity or also it can lead to permanent dysfunctions and in some cases, patients may not recover from the adverse event. IrAEs not only affect the immunotherapy rechallenge, they may also impact in the potential subsequent antineoplastic treatment that the patient will receive, especially if the patient does not recover the adequate organ function, and finally, they can impact on patients survival.

Despite this, recent publications have reported a relationship between irAEs and clinical efficacy in cancer patients in terms of response rate, PFS and OS (23).

In the case of lung cancer, a comprehensive retrospective study trying to identify biomarkers of long-term responders in advanced NSCLC patients that received ICI, suggests the presence of irAEs as a prognostic factor for better survival (24). In the same line, another publication of NSCLC patients treated with nivolumab in advance setting, has shown that the development of irAEs is associated with better PFS [9.2 months(m) vs. 4.8 m; HR = 0.52] and OS (NR vs. 11.1 m; HR = 0.28) (25). Similarly, positive association between irAEs and survival outcome has been demonstrated in a large cohort of NSCLC Italian patients treated with anti-PD1 agents. Specifically, higher ORR, longer PFS and longer OS were observed in patients who developed irAEs compared to those who did not. Of note, the median OS (mOS) in patients with irAEs was 20.50 vs. 8.5 m, irrespective of the type of irAE (26). In a retrospective French cohort of 270 patients the outcomes were also better in patients with irAEs, showing an OS NR vs. 8.21 m, respectively (HR = 0.2); the PFS was 5.2 vs. 1.97 m (HR = 0.42); and ORR was 21.3 vs. 5.7% (27). Similar data has been observed in an Asian study about patients treated with ICIs in which DFS is higher in the subset of patients who developed toxicity (28). Other similar series have been published reporting similar outcomes (29, 30).

Moreover, in NSCLC setting the influence of multisystem irAEs in survival has been researched and the presence of an irAE in more than one system or organ is associated with improved survival (21).

Also in melanoma cancer patients, a relationship has been described between irAEs and clinical outcomes. Longer mOS has been reported in melanoma patients treated with ICIs who presented toxicity compared to those who did not (21.9 vs. 9.7 m), respectively (31). Higher disease control rate has also been reported in patients with irAEs (69.8 vs. 49.3%) (32). In a real-world cohort including almost 200 patients, a greater OS and PFS was observed in melanoma patients who experienced irAEs than in those who did not, with reported data of NR vs. 9 m and 28 m vs. 5 m, respectively (33).

Focusing on the severity of the toxicity, a Canadian cohort of advanced melanoma patients treated with anti-PD1 agents observed a mOS of 39 vs. 23 m for any irAE and no irAE, respectively, and mOS NR vs. 29 m for grade $\geq$ 3 irAEs and no grade $\geq$ 3 irAEs, respectively (34).

Despite this data, some studies have reported controversial results regarding the association between irAEs and efficacy with ICI, showing no statistically significant better outcomes in patients with toxicity (35) and similar ORR (58.3 vs. 50.2%) (36).

In other solid tumors, this interaction between toxicity and results, has been confirmed. A retrospective study which included renal cell cancer patients demonstrated better PFS in patients with irAEs, although this benefit was not reflected in OS (37). In a study in renal cell cancer patients treated with anti-PD1 agents, a greater OS was reported for patients experiencing toxicity vs. those without toxicity (35.9 vs. 26.5 m, respectively) (38).

In head and neck cancer and gastrointestinal tumors, better outcomes have been reported too in those patients with irAEs vs. those without toxicity (39, 40).

Lastly, a meta-analysis which includes most relevant studies of different types of tumors has demonstrated a positive association between irAEs and survival regardless of the localization of the primary tumor, type of ICI and irAE (41).

Table 1 summarizes the results about the impact of irAEs and corticosteroids in terms of PFS and OS in the different types of tumors.

TABLE 1 | Type of tumor and OS, PFS of different studies.

Type of tumor	References	OS (months)	PFS (months)		
		irAEs	Without irAEs	irAEs	Without irAEs
NSCLC	Haratani et al. (25)	NR	11.1	9.2	4.8
	Cortellini et al. (26)	20.5	8.5	10.1	4.1
	Grangeon et al. (27)	NR	8.2	5.2	2
	Ahn (42)	24	11.6	7.4	3.3
	Ricciuti et al. (29)	17.8	4	8.5	2
Melanoma	Indini et al. (31)	21.9	9.7	NA	NA
	Bastacky et al. (33)	NR	9	28	5
	Sou et al. (34)	39	23	NA	NA
Renal cell	Labadie et al. (37)	NA	NA	20.5	10.1
	Elias et al. (38)	35.9	26.5	17.8	6.6
Head and neck	Foster et al. (39)	12.5	6.8	6.9	2.1
Gastrointestinal	Das et al. (40)	32.4	8.5	32.4	4.8

IMPACT OF STEROIDS, IMMUNOSUPPRESSIVE TREATMENT AND ANTIBIOTICS IN CLINICAL OUTCOMES IN PATIENTS WHO DEVELOP IRAES

Corticosteroids are the mainstay in the management of toxicities produced by immunotherapy but in some cases the management of the toxicity does not require their use. It is known that the use of corticosteroids produces immunosuppression that could lead to tumor progression. However, whether the patients who needs steroids to manage the irAE have different prognosis compared to those who do not remains an unanswered question.

In order to investigate this point, a metanalysis was recently published suggesting a worse OS in patients taking steroids for supportive care reasons, but if the purpose of the treatment is to manage adverse events related with immunotherapy the OS was not affected (43).

These data are consistent with another study including different types of tumors. They observed that patients with irAEs that required steroids presented higher PFS but no differences in OS (44).

Following the same line, patient survival has not been affected by the use or not of immunosuppressants in the context of toxicity due to immunotherapy in patients with melanoma (45).

In conclusion, the published data suggest that the use of steroids to manage irAEs does not impact in the survival of the patients.

Antibiotics may also be potentially useful in treating irAEs. Antibiotics therapy led to an antibiotic-associated dysbiosis that appears to be detrimental to ICI efficacy (46). Several studies have evaluated this situation, but the evidence on the impact of antibiotics used to treat an irAE on the benefit of immunotherapy is much more limited (47). In a recent systematic review and meta-analysis, OS and PFS in patients treated with immunotherpy were negatively associated with the use of antibiotics but varies significantly between different types of tumors (48).

However, these conclusions about the impact of corticosteroids and antibiotics on ICIs benefit must be interpreted with caution due to the retrospective design and the low level of evidence of the majority of the studies published on these topics.

DISCUSSION

Diagnosis and management of irAEs is challenging and requires continuously updated diagnostic and monitoring tools.

Given that different immune checkpoint inhibitors may have distinct mechanisms of action, the incidence, severity and the tissue affected may vary.

The incidence of irAEs upon ipilimumab treatment (anti-CTLA4) is dose dependent, with up to 80% of patients experiencing some adverse events when treated at a dose of 10 mg/kg (49). Rates of irAEs with anti-PD-1/PD-L1 treatment are similar to those anti-CTLA4 and range from 70 to 85% but severe toxicities (G3-4) are less frequent (50).

Several factors can impact on ICIs treatment outcome. irAEs and their treatment are one of the most studied.

This is especially important given that the immune mechanisms involved in disease control are, in many cases, very similar to those that trigger immune-mediated toxicities. Therefore, treating the secondary effects can generate a decrease in immune activity and, as a consequence, a lower efficacy of the treatment (51).

The development of an adverse effect may have multiple consequences. The inflammation of the organ or tissue can be permanent and lead to organ failure. In addition, toxicity may be associated with clinical deterioration of the patient. All of this can limit or condition the use of subsequent treatments and impact the patient's survival and quality of life. However, with irAEs, this negative impact of permanent sequelae, is under debate and is conditioned by different factors and clinical situations.

Corticosteroids and antibiotics are the most commonly prescribed medications for the treatment of AEs during

immunotherapy and both of them can impact on ICIs treatment efficacy.

Due to their immunosuppressive effects, treatment with corticosteroids is associated with worse outcomes in terms of efficacy (52). However, the time at which they are initiated and the reason for which they are prescribed seem to play a role in the consequences of their use on the disease control.

When administered to control the symptoms of the disease, they have a negative effect on the efficacy that does not seem to be equally obvious when they are used in the context of an irAE (53).

Further research is needed to improve the knowledge about the interactions created between the different checkpoints involved in the immune response. Due to this increasing complexity, a multidisciplinary team is necessary to ensure an optimal management of these toxicities that can become serious and/or permanent.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Predictive Biomarkers of Severe Immune-Related Adverse Events With Immune Checkpoint Inhibitors: Prevention, Underlying Causes, Intensity, and Consequences

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Immune checkpoint inhibitors (ICIs) have dramatically transformed oncology by prolonging overall survival and yielding better patient tolerance compared to other chemotherapeutic agents. However, numerous questions remain unanswered about the toxicity profile of ICIs, its relationship with the treatment response, and causes underlying the excellent treatment response in some patients, while recalcitrance in others. Research groups have continued to seek biomarkers that may permit the identification of treatment responders and predict toxicity to facilitate cessation of immunotherapy before the development of severe toxicity. However, some studies have found associations between serious adverse events and longer survivorship. The research question entailed determining whether a biomarker is needed to predict severe immune-related adverse events prior to their development or whether providing early treatment for toxicity would inhibit the immune system from attaining a long-lasting anti-tumor effect. Therefore, this review conducted an in-depth analysis into the molecular basis of these observations.

Keywords: immune checkpoint proteins, immune-related adverse event (irAE), biomarker, autoimmunity, severe toxicity

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have sparked a massive revolution in oncology. Immune checkpoints are a group of membrane receptors present on cytotoxic T lymphocytes whose function is to prevent an indefinite immune response that could severely damage healthy host tissue. Programmed cell death protein 1 (PD1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) are the most studied immune checkpoints. ICIs are monoclonal antibodies that target PD-1/programmed death ligand 1 (PD-L1) or CTLA-4, reactivating the anti-tumor immune response that is inhibited by the overexpression of these proteins by tumor cells (1). However, not all patients respond to immune checkpoint blockade. Response rates range from 13 to 40%, depending on monotherapy or combination treatment and the primary tumor (1). Hence, it imperative to discover biomarkers that can aid in predicting the treatment response to avoid the administration of ineffective drugs, which are also exorbitantly expensive. Despite tremendous efforts in this field, PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability are the only predictors available for use in routine clinical practice (2), although their specificity is not ideal.

Moreover, even though the toxicity profile of ICIs is better than that of chemotherapy, the rate of adverse effects is significantly high with ICIs. Severe treatment-related toxicity was observed in 55% of patients treated with the combination of PD-L1 and CTLA4 inhibitors (3) (grades 3–4 according to the Common Terminology Criteria for Adverse Events version 5) (4). Colitis, rash, and hypophysitis are the most frequent adverse effects of CTLA4 inhibitors, whereas arthralgia, pneumonitis, vitiligo, and hypothyroidism are most frequent with PD-L1 inhibitors (5), with high temporal unpredictability (6). However, some studies have shown that immune-related adverse events (irAEs) could be predictors of the anti-tumor response (7, 8).

The individual irAEs evoked by ICIs bear striking similarities to classic autoimmune diseases (9),with the main bulk of evidence being focused on immune-related colitis (10, 11). The mechanisms that trigger irAE development are incompletely understood, but are chiefly related to the loss of peripheral tolerance and increase in self-reactive T-cell clones (12). They are often poorly reported in clinical trials, and until recently, principal knowledge about their development was derived from the retrospective studies, whose *a posteriori* nature precludes the collection of samples and analysis of possible triggers. Usually, irAEs develop in 1 organ at a time and are considered to be dose independent; however, with anti-CTLA4, recent studies show differences depending on the administered dose of ipilimumab (13). Moreover, irAEs can appear even months after cessation of the drug, which may be challenging to identify and treat in routine clinical practice (6, 12).

The initial treatment for severe irAEs entails the administration of high-dose corticosteroids (specifically, methylprednisolone 1 mg/kg/day) (3, 14). Other immunomodulators, such as infliximab, vedolizumab, tocilizumab, mycophenolate, etc., can be added, if the irAE cannot be controlled with corticosteroids alone (**Table 1**). Usually, treatment must be stopped if the patient develops severe toxicity, but it is not always linked to cessation of the anti-tumor benefit, and may even have the opposite effect, i.e., years of recurrence-free survival without any treatment (15). However, other patients experience an explosion of disease after the administration of high-dose corticosteroids or other immunosuppressants (16). Therefore, this treatment was initially contraindicated in patients treated with ICIs, because an abrupt loss of effectivity was anticipated (17).

The principal hypothesis that motivated this research is whether a biomarker should be sought to predict severe irAEs prior to their development, or if early treatment for toxicity will inhibit the immune system from attaining a long-lasting anti-tumor effect. This study delved into the molecular basis of these observations, reviewed the pathogenesis of irAEs, and sought biomarkers that could specifically predict severe toxicity. Furthermore, it attempted to elucidate the molecular link between toxicity and the anti-tumor response, and discussed the need for these biomarkers in clinical settings and the implications of possible preventive treatment for irAEs.

IMMUNE-RELATED ADVERSE EVENTS: MOLECULAR BASIS

Immune checkpoints play a fundamental role in maintaining immunologic homeostasis (6). Therefore, the blockade of these checkpoints may increase the anti-tumor activity of the immune system, which is accompanied by the risk of the loss of self-tolerance, leading to the occurrence of irAEs, causing damage to normal cells and tissues.CTLA4 modulates the immune response in theearly stages, while PD-1 acts later in the immunologic cycle (1, 12). CTLA-4 blockade induces expansion of the inducible T-cell costimulatory Th1-like CD4 effect or as well as exhausted-like TCD8+ cells, while PD-1 blockade primarily induces expansion of exhausted-like tumor infiltrating TCD8+ cells (18).

The deficiency of CTLA-4 leads to severe autoimmune diseases (colitis and myocarditis) characterized by T-cell infiltration in murine models. This phenomenon also occurs with the loss of PD-1, but is less straight forward with genetic strain differences, and may be accompanied by the development of late-onset autoimmune diseases (such as lupus-like disease) (19).

The self-tolerance of the immune system, in which regulatory T (Treg) cells play a fundamental role, can be lost in several ways. Tregs are a subgroup of CD4 + T lymphocytes that maintain immune tolerance. Usually, a higher count of Tregs in peripheral blood is related with poor prognosis for several cancers (20). Nuclear factor kappa B (NF-κB) activation is essential for Treg-induced homeostasis, and Treg and effector T-cell expansion (21). Constitutive activation of NF-κB-induced kinase (NIK) on Tregs induces alteration of its functions and genetic signature (GITR+CD25+Foxp3+), leading to development of autoimmune diseases (20). CD25+ T and CD25– lymphocytes inhibit the development of autoimmunity, which could also be evoked by FOXP3 expression, which, in turn, increases Treg and M2 macrophage infiltration (immunosuppression), tipping the balance in favor of the tumor cells. Polymorphisms in the Foxp3 locus affect Foxp3 expression and can influence Treg cell function (22). The increase in NOTCH3 also plays a role in decreasing the TMB, the GEP-gene expression profile scores, and the TCD8+ activated lymphocytic infiltration. This mechanism is correlated with adenosine 2A receptor (ADORA2A) and CD276 (B7-H3) expression (23), both of which possess potential therapeutic effects (24, 25). Adenosine, which is generated in the tumor microenvironment (TME), inhibits the anti-tumor function of various immune cells, such as cytotoxic T cells and natural killer (NK) cells. Moreover, ADORA2A is implicated in the upregulation of inhibitory cytokines, such as transforming growth factor-beta (TGF-β) and inhibitory receptors, such as PD-1 itself. Interactions with FOXP3 stimulate the transformation of CD4+ T-cells into Treg cells, thus inhibiting the immune response (26).

Furthermore, T-cell activation is markedly sensitive to the depletion of glutamine and glucose, and the exogenous uptake of serine and alanine (27). Effect or T cells are consequently sensitive to the oxidative stress in the TME, which can induce the exhausted phenotype (27), which may be implicated in response and toxicity.

TABLE 1 | Management of the most frequent severe irAEs (14) and biomarkers that may predict them.

irAEs, all grades (% PD-L1/ CTLA-4/ combination) Median time to onset (41)	Common management (grade ≥3) (14)	Special management considerations (14)	Biomarker: immune cells		Biomarker: cytokines (↑ except indicated)	Other potential biomarkers
Colitis (<19, 13–54, 29) 38 days	Consider patient admission	Infliximab or vedolizumab	↑CD4TH17 ↓Tregs (41, 42) ↑CD177 and CEACAM1 genes (46)		IL-17 (31, 42) ↓ IL-6 (31) IL-8 (31, 42)	Microbiome (21, 79) ↑Faecalibacterium, ↑Firmicutes, ↓Bacteroidetes (colitis)
Dermatitis Incidence of all dermatological irAEs: (17–37, 37–70, 48) 25 days	Steroids 1–2 mg/kg/day until grade 1, followed by a tapered dose for 4–6 weeks*	Topical emollients, corticosteroids, oral antihistamines Consider phototherapy	-	↓Circulating B cells ↑CD21^{lo} B cells/plasmablasts (44)	IL-6 IL-10 (19)	TGFβ signature (58) NLR (better accuracy for pneumonitis) (80) Eosinophils (41) Lymphocytes >2000 (41) Sarcopenia (58) Body mass index (60) Vitamin D (on investigation)
Arthritis (6–12, 5, 11) 3 months	Consider indefinite suspension of the drug *	Long- term administration of TNF inhibitor or consider tocilizumab (81)	↓CD8 effectors (12)		IL-6	
Pneumonitis (<1, 2,7, 10) 3 months		Infliximab or mycophenolate mofetil IV/IVIG or cyclophosphamide	↑CD4 TH2 (12)		-	
Thyroid disorders Hypothyroidism (6, 4, 13), Hyperthyroidism (3, 2, 8) 14–73 days		Hold the drug until symptoms resolve to baseline with appropriate therapy Consider IV levothyroxine for myxoedema, steroids and supportive care	↑CD4 TH17 (12)		-	

*Except thyroid disorders.

(% PD-L1, CTLA-4, or a combination of the 2): Percentage of incidence of these irAEs according to the administered drug(s) (41).

irAEs, immune-related adverse events; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; NLR, neutrophil to lymphocyte ratio.

However, T cells are not the only protagonists involved in the development of irAEs. The possible role of cytokines and other immune cells involved in the maintenance of self-tolerance, and consequently, irAE development, such as the previously mentioned NK cells, B cells, and autoantibodies, which are products of the humoral immune system, should not be forgotten.

First, cytokines such as the IL-12 family (IL-12, IL-23, IL-27, and IL-35) may be related to both tumor immunity and autoimmunity, necessitating examination of their modulation in irAEs (28). The other cytokines related to immune inhibition include IL-10, IL-4, IL-6, and IL-13 (1), and TGF-β, which is correlated with FoxP3 expression and T-reg infiltration and immunesuppression in some models (29).

Second, given that autoantibodies are associated with the development of some autoimmune diseases, such as Hashimoto's thyroiditis and rheumatoid arthritis, autoantibodies can be considered as a potential cause of irAEs (30). However, not all antibodies play a role in the pathogenesis of irAEs.

Therefore, the development of irAEs could be related to the following mechanisms: surge in T cell activity against antigens that are present in tumors and healthy tissue, elevation in the levels of pre-existing antibodies or inflammatory cytokines, or enhancement of complement-mediated inflammation due to direct binding of anti-CTLA4 antibodies with CTLA4 expressed on normal tissue (6). These interactions could cause cellular toxicity via antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity (9).

The molecular basis of irAEs differs depending on the individual drug (31). Usually, anti PD-1toxicity is mediated by auto antibodies that already exist in patients and are stimulated after the initiation of ICIs (32). Therefore, irAEs, such as thyroid disorders or vitiligo, are more frequent with anti-PD-1/PD-L1 drugs. Hence, we may infer that patients with a history of spontaneous autoimmune diseases would experience irAEs with greater frequency and (possibly) greater severity, which may or may not be related to the underlying autoimmune disease. The findings of studies and case reports in this regard were controversial (33–36). The reported frequency of disease flares was higher with anti-PD-1/PD-L1 drugs (62 vs. 36%), while that of *de novo* irAEs was higher with ipilimumab (42 vs. 26%), which could be related to the previous observation on autoantibodies (37). However, although irAEs and flares are frequent among patients with autoimmune diseases (especially those with rheumatoid arthritis), their toxicities are usually manageable even without cessation of ICI therapy (38). Further evidence and guidelines are required in the future to fully understand the mechanisms underlying irAEs and autoimmunity, and advise clinicians on the safe prescription of ICIs in this context.

We must reiterate that some irAEs appear more frequently when ICIs are used for the treatment of specific tumors, albeit not in all patients. For example, the incidence of vitiligo is higher in patients with melanoma (39). Since ICIs increase the anti-tumor response via melanocytes, it is not surprising that the occurrence of vitiligo may be associated with an increased anti-tumor response (6, 40).

Colitis is another example highlighting how the development of different irAEs depends on the culprit drug. If the irAE is induced by anti-PD-L1, CD8+ T lymphocyte infiltration is observed in the intestinal mucosa, whereas irAEs caused by anti-CTLA4 are characterized by the predominance of CD4+T cells and elevation in TNF-α levels (11). Lower levels of TNF-α in the intestinal mucosa are related to better sensitivity to corticosteroids (11).

BIOMARKERS FOR SEVERE TOXICITY

We sought biomarkers to predict irAE occurrence before their induction, in order to facilitate early treatment to avoid severe (grade 3) and life-threating (grade 4) toxicity. The more promising ones are mentioned in this section, although none of these have been validated yet, and larger prospective studies focusing on this aspect are vital.

The first potential biomarker is related to enhanced T-cell activity against antigens present in tumor and healthy tissue; specific TCR sequences predispose cancer patients to organ-specific toxicities. For example, a lower proportion of CD8+ effector cells is associated with arthritis, while a higher proportion of CD4 TH2 cells and CD4 TH17 cells at baseline is related to pneumonitis and thyroiditis, respectively (12). It is logical to infer that a reduction in the proportion of Tregs could be related to higher toxicity, but limited data is available on its predictive ability for colitis (41, 42). Thus, the future direction for tumor immunotherapy lies in enhancing the function of tumor-specific T cells rather than that of other T-cell subtypes (43).

Furthermore, circulating B cells may be useful for predicting irAEs. Patients with melanoma treated with ICIs who experienced a 30% or greater reduction in the baseline levels of total circulating B cells, and increase in $CD21^{lo}$ B cells or plasma blasts, were significantly more likely to develop high-grade IRAEs than those without B cell changes (44). Interestingly, PD1 expression was higher in $CD21^{lo}$ B cells (45). Further studies are needed to validate these observations.

Additionally, the infiltration of digestive neutrophils into the colon during treatment is associated with digestive toxicity with anti-CTLA-4, in addition to the increased expression of the CD177 and CEACAM1 genes, which are markers of neutrophil activation (46).

First, the following useful biomarkers should be mentioned, which are simple and inexpensive to detect the neutrophil to lymphocyte ratio, which is elevated in patients who develop grade 3 and 4 pneumonitis and colitis after anti-PD-1;the absolute eosinophil count, which increases before the onset of >grade 2 endocrine disorders; and the absolute lymphocyte count (>2,000/mL). These parameters are related to irAEs, albeit without any specificity (41, 46), and can be easily altered with the incidence of other conditions such as infectious diseases, which may alter prognostication.

Second, humoral biomarkers should also be considered, since elevated levels of pre-existing antibodies or inflammatory cytokines act as triggers for the development of irAEs; IL-6, IL-17, and sCD163 are significantly associated with irAEs in cancer

patients treated with ICIs (7, 47). CD4 TH-17 cells secreting IL-17, IL-6, and IL-8 appear in patients who develop grade >3 colitis (with anti CTLA-4) (42, 46). The elevated levels of IL-6 and IL-10 are also linked with dermatological irAEs (19), while lower levels of IL-6 are reportedly associated with colitis (31).

Although the higher levels of autoantibodies have been linked to the irAE development, the relationship between auto antibodies and the pathogenesis of toxicities is unclear. Enhanced T-cell activation may be the most plausible trigger for irAEs, while the humoral immune system may play a supporting role. These phenomena can be measured using protein microarrays, akin to those for autoimmune diseases (48). However, anti-thyroid peroxidase (49) is the only antibody that can be employed in routine in daily clinical practice to predict irAEs. Furthermore, recent studies have found no association between baseline auto antibodies and irAE severity (30). These findings have precluded their use for the prediction of severe toxicity, and consequently, prophylactic treatment.

Finally, a few studies have posited gene signatures as a potential predictive measure for irAE incidence and severity, at least for immune-related colitis (50). A strategy that combined pharmacovigilance data with omics data identified 2 additional potential biomarkers associated with the use of PD-1/PD-L1 agents, viz. lymphocyte cytosolic protein 1, which is involved in T-cell activation, and adenosine diphosphate dependent glucokinase, which mediates the metabolic shift during T-cell activation (51). Nevertheless, these findings were derived from a small sample, and further investigations are needed to validate these biomarkers.

The microbiome, as well as body mass index (BMI) and body composition, are the two intriguing potential biomarkers under investigation.

Fecal microbiome transplantation (FMT) has emerged as a treatment for immune-related colitis. A study showed reconstitution of the gut microbiota and elevation in Treg cells within the colonic mucosa with FMT (52). The baseline gut microbiota enriched with Faecalibacterium and other Firmicutes were found to be associated with the clinical response and CTLA-4-induced enterocolitis (42). The 2 studies reported that a low abundance of Bacteroidetes was associated with colitis. Nevertheless, to date, the studies that analyzed this issue have included a small patient population. A larger prospective studies exploring other toxicities besides colitis are needed and some of which are already underway (53).

Furthermore, recent studies show that variations in the gut microbiome have the potential to enhance the therapeutic response and reduce the irAEs associated with ICIs in multiple cancers (54, 55). The gut potential function of intestinal microbes as an immunemodulator (by increasing the anti-tumor effect and potentially reduce irAEs) is so considerable that some ongoing trials are investigating the possibility of combining them with anti PD-1/PD-L1 and anti-CTLA-4 drugs (21). The relationship of certain bacteria with vitamin B and poly-amine transport to the gastrointestinal tract may be the mechanism underlying the increased efficacy of immunotherapy in the background of the predominance of certain bacteria (56). The differences in the microbiome may apparently be responsible for toxicity or response, depending on the drug. Bacteroides fragilis, Burkholderia cepacia and the Faecalibacterium genus are associated with better response and lower incidence of colitis with anti-CTLA-4, while Bifidobacterium breve and longum, Akkermansia muciniphila, and Faecalibacterium prausnitzii are related with better outcomes with anti-PD-1/PD-L1 (56). The microbiome and its modifications may be responsible for the negative impact of some antibiotics on survival outcomes in patients receiving ICIs (57).

Another important biomarker that may be related to worse outcomes with anti-PD-1 treatment is sarcopenia. Several possible explanations exist, such as the implication of TGF-β and IL-6 and the development of chronic inflammation that results in cancer immune evasion through T cell exhaustion (58). Sarcopenia is related not only to poorer survival outcomes, but also to a higher incidence of irAEs (58). Besides, obesity has been linked with poorer outcomes with classic chemotherapy, but is apparently associated with improved outcomes in patients treated with ICIs (obesity paradox) (59). This association was especially marked when BMI and irAEs were considered in combination, meaning that the observed therapeutic benefit is further enhanced in the event of irAEs in the overweight population (60). Further studies are needed to analyse the cytokines that could be involved, as obesity is related to inflammation and metabolism, and its relationship with the hallmarks of cancer and immunotherapy requires investigation.

As mentioned above, the studies have that link potential biomarkers with irAEs are limited by their small sample size, and the unpredictable onset and frequency of these adverse events poses a challenge for the design of larger (much needed) prospective trials.

TOXICITY ITSELF AS A BIOMARKER

Several studies have reported a positive association between the incidence of irAEs and the survival outcomes (6, 61, 62), while others have found no such association (63). A systematic review and meta-analysis has shown that grade ≥3 toxicities were correlated with a better overall response rate, but poor overall survival (64), while another has linked irAEs with better survival and response (7).

It is possible that certain immune-related adverse events possess a more direct relationship with anti-tumor efficacy than others (6), e.g., vitiligo in patients with melanoma. Thus, the irAEs could act as biomarkers themselves; however, since the intensity of irAEs cannot be modulated at present, nor can their severity be predicted before onset, irAEs cannot be uses as biomarkers of response. Doing so would jeopardize the patient by blindly exposing them to life-threatening adverse effects, owing to the lack of effective treatments that do not compromise the anti-tumor effect.

Furthermore, a few attempts were made at administering preventive treatment for the irAEs, which have been unsuccessful (65). However, it is debatable whether this could be attributed to the lack of efficacious preventive treatment or the utilization of a suboptimal biomarker.

DISCUSSION AND FUTURE DIRECTIONS

This review assessed several potential biomarkers for severe toxicity evoked by ICIs; however, it could not conclusively identify a definite predictive biomarker for the timing of onset and occurrence of irAEs. Unfortunately, these data do not provide sufficient evidence to design a trial that can provide early treatment modalities for irAEs. Besides, considering the potential relationship between irAEs and tumor response, attempts to stop the onset of irAEs before they effect the modifications in the immune system needed to achieve longer survival may deprive patients of the potential long-term and ulterior benefits.

The future of oncological medicine lies in immunemodulation, and in line with this approach, other options should be explored for the treatment of irAEs that do not involve the use of corticosteroids, owing to their ambiguous effect on the anti-tumor activity of the immune system, if they are not administered at the optimal time, and substantial toxicity for patients (osteoporosis, infections, hypertension, hyperglycaemia, etc.) (66, 67).

Moreover, any discussion on the discovery of immunemodulators should include not only new combination drugs, but also physical activity (PA), vitamin D, and metabolism.

First, by virtue of reducing hypoxia and normalizing the tumor vasculature (68), PA can modify the TME and significantly reduce tumor aggressiveness (69). Moreover, PA induces transformations in the AKT and mTOR pathways, muscular IL-6, and mitochondrial function, which consequently inhibit tumor cell proliferation (68). Furthermore, PA stimulates NK cells by preparing the TME for their arrival, increasing the expression of NKG2D and NKp46 receptors (70). PA can increase the cytotoxic activity of T cells and macrophages, thus lowering the risk of metastasis (69). These modifications are also observed in patients who respond better to ICIs (71–73). Hence, it seems feasible that PA could act as a potential coadjuvant to immunotherapy, as already observed in pre-clinical models (74).

The potential of vitamin D as an immune modulator has also garnered interest. Vitamin D seem to benefit patients with autoimmune diseases; considering that irAEs share some characteristics with them, it is reasonable to assume that vitamin D may be useful for treating or even preventing their development (75, 76). Furthermore, vitamin D may play a role in the expression of PD-L1, owing to its vast immunemodulation potential. Moreover, as patients with cancer usually have vitamin D deficiency, regular testing, and examining its relationship with the development of irAEs could be an interesting direction for research. In fact, some ongoing studies have already focused on this aspect (ClinicalTrials.gov Identifier: NCT04615988).

Furthermore, the epigenetic role of metabolism on the immune system cannot be ignored (27). Exhausted T lymphocytes inhibit the AKT and mTOR pathways, stimulating fatty acid oxidation and increasing reactive oxygen species levels, and consequently, modifications in the exhausted T lymphocytes (77). However, active T lymphocytes mainly derive energy from glycolysis even in the absence of oxygen, which is inhibited by PD-L1, at least in chronic infections, but could also be relevant for neoplasms (77). The mitochondria play a fundamental role in this mechanism, and their potential involvement in the treatment for chronic infection and tumor control is being studied. Finally, the methylation pattern for exhausted T lymphocytes has been described, which seems to confer resistance to immunotherapy (78), making this mechanism a possible focus for future investigations.

In conclusion, it is clear that future research in the fields of immunotherapy and cancer is going to take a complex route, and an independent biomarker that can predict response, toxicity, or resistance to immunotherapy is not feasible. However, the results from studies on the new immune modulators may eliminate the need for high-dose corticosteroids. Their effects on the immunesystem, which are complex and sometimes contradictory, have an immenseimpact on toxicity, which cannot be allowed in this era of high precision medicine. We should guide our efforts to attempt to modulate the immune response to achieve better survival outcomes even without the development of irAEs.

AUTHOR CONTRIBUTIONS

AC-G wrote the manuscript and ML approved the final version. All authors contributed equally to the bibliographic research for this work. All authors contributed to the article and approved the submitted version.

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REVIEW
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Immunotherapy and the Spectrum of Kidney Disease: Should We Individualize the Treatment?

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The new targeted cancer therapies including immune checkpoint inhibitors (ICIs) have been demonstrated to improve the survival of oncological patients, even in cases of metastatic cancer. In the past 5 years, several studies have revealed that ICI can produce several immune-mediated toxicities involving different organs, such as the skin, the gastrointestinal tract, the liver, and, of course, the kidney. The most frequent lesion of immunotoxicity in the kidney is acute interstitial nephritis (AIN), although other nephropathies have also been described as a consequence of the use of ICI, such as glomerulonephritis and acute thrombotic microangiopathy, among others. In addition, kidney rejection has also been reported in kidney transplant patients treated with ICI. Normally randomized clinical trials with ICI exclude patients with end-stage kidney disease, namely, patients undergoing dialysis and kidney transplant patients. Several important questions need to be addressed in relation to immunotherapy and patients with kidney disease: (a) when to start corticosteroid therapy in a patient with suspected acute kidney injury (AKI) related to ICI, (b) the moment of nephrologist referral and kidney biopsy indication, (c) management of ICI in patients undergoing dialysis, and (d) the effect of ICI in kidney transplantation, immunosuppressive personalized treatment, and risk of allograft rejection in kidney transplant patients. The objective of this review was to summarize the recently published literature on a wide spectrum of kidney disease patients with cancer and ICI. This review will address three main important groups of individuals with kidney disease and cancer immunotherapy, AKI associated with ICI, patients undergoing dialysis, and kidney transplant recipients. We believe that the information provided in this review will enlighten the personalized ICI treatment in individuals with a broader spectrum of kidney diseases.

Keywords: dialysis, chronic kidney disease, renal transplant, immunotherapy, renal biopsy

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INTRODUCTION

Cancer is an important cause of death worldwide and is expected to be the first cause of death in many countries in years to come since stroke and heart disease show a decrease in mortality (1). According to the data provided by the World Health Organization (WHO) in 2019, cancer was the first or second cause of death in subjects below 70 years in 112 out of 183 countries, and it

ranks third or fourth in other 23 countries (2). Thus, in 2020, 19.3 million new cases of cancer were diagnosed and 10 million deaths were recorded worldwide (1). The increase in the incidence and mortality of cancer has been mainly related to aging of the population and the increase in risk factors for the development of cancer (1). Given the important incidence of cancer, the scientific community has made efforts in recent years to develop new therapies for these patients. One of the emerging therapies is under the premise of stimulating the patient's own immune system to deal with cancer cells: therapies based on vaccines, oncolytic viruses, T cell-directed therapies, bi-specific antibodies, and checkpoint inhibitors (3). With the use of these new therapies, an increase in patient survival has been evidenced (4). Thus, the tumor microenvironment is composed of various escape routes from the recognition of the immune system, which allows the growth and dissemination of cancer cells, causing metastasis. An important mechanism is the expression of inhibitory ligands for CTLA-4 and PD-1 receptors on T cells and other immune cells that cause inhibition of the tumor microenvironment, known as immune checkpoints that deactivate T cells (5). Here remains the pathophysiological mechanism of the use of immune checkpoint inhibitors (ICIs), which bind to CTLA-4 and PD-1 to activate immune cells from a quiescent state to cause a reaction against tumor cells (3). However, this mechanism is not selective, and the use of ICI increases the incidence of immune-related adverse events (irAEs). The gastrointestinal tract, the skin, the endocrine system, and the liver are the most frequent locations where irAEs occur, with an incidence that ranges between 15 and 90% (6, 7). The kidney may also be involved in the damage caused by irAEs with an estimated incidence of 3–5% (8–10). The kidney pathology most frequently associated with the use of ICI is acute interstitial nephritis (AIN), although cases of glomerulopathies and thrombotic microangiopathies, among others, have also been described (11). In patients with acute kidney injury (AKI) associated with ICI, it is crucial to know when to perform a kidney biopsy and to start treatment, since it has been shown that the time of starting treatment is important for kidney prognosis (12). As the use of ICI has demonstrated impressive results in patients with advanced cancer, their use has been increasing in recent years including people with a kidney transplant or with a chronic kidney disease grade 5 treated by dialysis (CKD5D). In kidney transplant patients, the use of ICI has been associated with an increased risk of acute rejection, making it necessary to individualize immunosuppressive therapy and close monitoring, especially if concomitant to kidney replacement therapy (KRT) (13). In addition, the use of ICI has also been extended to the population with CKD5D, including both hemodialysis (HD) and peritoneal dialysis (PD) therapy. However, in these two scenarios, experience is limited and the literature is scarce (14). Altogether, the spectrum of kidney disease is wide around the use of ICI, and different clinical situations of patients with cancer and kidney disease must be considered. The intention of this review is to address the entire spectrum of all kidney patients receiving ICI. For that purpose, the kidney complications derived from the treatment and its use in the renal population such as renal transplant patients and patients with CKD5D receiving KRT in the form of HD and PD will be addressed.

NATIVE KIDNEY INJURY ASSOCIATED WITH IMMUNOTHERAPY

As mentioned above, AIN is the most frequent (80–93%) histopathological lesion documented associated with ICIs in patients with acute kidney failure (8, 11, 15–19). Gupta et al. published a multicenter study enrolling a huge cohort of patients with AKI associated with immunotherapy: a total of 429 patients with AKI associated with a checkpoint inhibitor (ICI-AKI) were compared with 429 controls who received the same treatment but they did not develop any kidney complications (12). In this study, a total of 125 kidney biopsies (82.7%) were diagnosed with AIN, with a latency time of 16 weeks (8–32 weeks) before the start of the treatment with ICIs and AKI; however, the AKI episode occurred in the first year after starting treatment only in 11.4% of cases. It is important to take into account the presence of hematuria in almost 40%, pyuria in more than 50%, and proteinuria and increased blood eosinophils in 16.5% of patients. Several studies focused on assessing the risk factors for developing AIN. The following characteristics have been identified as risk factors for ICI-AKI: (1) the association with other drugs, which happens between 60 and 75% of cases (8, 12, 15), mainly proton pump inhibitors; (2) lower baseline estimated glomerular filtration rate (eGFR) (8, 12); (3) combined ICI therapy (8); (4) arterial hypertension (17); (5) prior or concomitant extrarenal irAEs such as rash and hepatitis as the most common (12, 17). Concomitant treatment with other drugs that increased the risk to develop AIN and the early start of corticosteroids in < 2 weeks are the most important factors for recovering kidney function in these patients (8, 12). In contrast, stage III of AKIN, lung cancer, and concomitant irAEs are risk factors for nonrecovery kidney function (8). In a recently published study by Garcia-Carro et al., the following were identified as risk factors for mortality: the type of cancer (not melanoma, lung, or urogenital malignance), the type of ICI, and the presence of an episode of AKI (20).

Glomerular diseases have also been described in patients with AKI associated with ICI treatment (**Table 1**) (8, 11, 12, 21–25). A large series of kidney biopsies was described in around 3–8% of the cases in some studies (12, 15) and in up to 41% of cases in another study, with a concomitant association of glomerulopathy and AIN (26). The glomerular pathology associated with ICI can be classified based on the clinical presentation: 1. the nephrotic syndrome as a clinical presentation of podocytopathies such as minimal change diseases or focal segmental glomerulosclerosis, amyloidosis, and membranous nephropathy and 2. the nephritic syndrome as a clinical presentation of pauci-immune vasculitis (11), complement 3 glomerulonephritis (G3GN) (24), immunoglobulin A nephropathy (27), IgA dominant postinfectious glomerulonephritis (23), anti-glomerular membrane disease, thrombotic macroangiopathy, immune complex glomerulonephritis, and lupus-like nephritis (25). The most frequent pathologies described are pauci-immune vasculitis

TABLE 1 | Glomerulopathies and ICIs.

Case	Renal manifestation	Therapy	Response
Clinical features of patients receiving anti-PD-1			
Daanen (21)	Nephrotic syndrome FSGS	DI + Steroids + MMF	Remission flowed by proteinuria relapsed
Kitchlu (22)	Nephrotic syndrome MCD	DI + Steroids	Partial remission
Mamlouk (11)	Membranous nephropaty	DI + Steroids	Remission
	IgA. Non proliferative lesions	DI + Steroids + MMF + Infliximab	Partial remission
	Focal necrotizing pauci-immune glomerulonephritis no crescents	DI + Steroids + plasmapheresis + Rituximab	Partial remission
Jung (23)	IgA dominant postinfectious glomerulonephritis	DI + Steroids + RRT	Remission
Cortazar (8)	Pauci-immune GN ANCA negative	Steroids + Rituximab	Remission
Ashour (24)	Diffuse endocapillary proliferative GN with cellular crescents Complement 3 glomerulonephritis	DI + Steroids	Partial remission
Gupta (12)	AA Amyloidosis	Tocilizumab	No recovery
	Membranous with lupus-like features	IVIG	No recovery
Clinical features of patients receiving anti-CTLA4			
Mamlouk (11)	Nephrotic syndrome. Endocapillary hypercellularity	DI + Steroids	Remission followed by relapsed
Gupta (12)	Pauci-immune GN	DI+Plasmapheresis + Rituximab	No recovery
Clinical features of patients receiving Anti CTLA4 + Anti PD-1			
Kitchlu (22)	MCD	DI + Steroids	Remission
Mamlouk (11)	Focal segmental pauci-immune glomerulonephritis with no cresents MPO + ANCA	DI + Steroids + Plasmapheresis + Rituximab	Partial remission
Fadel (25)	Extramembranous and mesangial deposits (IgG, IgM, C3 and C1q) and + ds DNA	DI	Partial remission
Clinical features of patients receiving Anti PD-L1			
Gupta (12)	Pauci-immune GN	Rituximab	No recovery

ICIs, immune checkpoint inhibitors; FSGS, focal segmental glomerulosclerosis; DI, discontinuation immunotherapy; MMF, mycophenolate mofetil; MCD, minimal changes disease; RRT, renal replacement therapy; IVIG: intravenous immunoglobulin.

(26.7%), podocytopathies (24%), and C3GN (11.1%) (26). The majority of these patients received corticosteroids (98%), and immunotherapy was discontinued (88%).

WHEN TO START CORTICOSTEROID THERAPY IN A PATIENT WITH SUSPECTED AKI RELATED TO ICI?

A few clinical guidelines have focused on the diagnostic and therapeutic management of patients with AKI secondary to the use of ICI (28–30) (**Table 2**). Due to the lack of studies on this topic or randomized clinical trials that evaluate the use of corticosteroids by comparing different doses and timings, our conclusion must be considered cautiously due to several potential limitations in the available data. To the best of our knowledge, currently, there are no randomized clinical trials for answering the proposed questions, and for that reason, the level of evidence for recommending when to start or tapering steroids in these patients is only based on published daily clinical practice and guidelines. Kidney damage can occur with a decline in kidney function and/or the presence of proteinuria. If proteinuria is < 1 g, the recommendation is to continue with the same dose of ICI and monitor and follow up (30). If proteinuria is 1–3.5 g/24 h, kidney biopsy should be considered, especially in cases of persistent proteinuria or progressive increase, and ICI therapy should be stopped until histological confirmation of a possible glomerulopathy. Once diagnosed, glomerulopathy treatment and the possibility of ICI reintroduction will be based on physiopathology. In the case of acute kidney function decline, the current guidelines recommend the clinical decision depending on the level of deterioration: if creatinine increases between 1 and 1.5 times the basal level, ICI should be stopped, dehydration corrected, and all potential nephrotoxic drugs should be avoided. Kidney function monitoring should be performed between 3 and 7 days (28–30). If the increase in creatinine is between 1.5 and 3 times the baseline level, the ICI should be stopped (28–30). The start of corticosteroids at a dose of 0.5–1 mg/kg is also recommended. If the deterioration is more severe, such as an increase of more than 3 times the basal level, the ICI should be definitively stopped and corticosteroid therapy should be started at a dose of 1 or 2 mg/kg. In the cases that do not respond to

TABLE 2 | Recommendations of clinical guidelines (NCCN Guidelines for Management of Immunotherapy-Related Toxicities and American Society of Clinical Oncology (ASCO) guidelines) (33, 34) in AKI in patients treated with immunotherapy.

Clinical conditions	Management	Treatment
Mild cases		
sCr 1–1.5 x baseline	Withhold ICI Monitor renal function every 3–7 days	Correct dehydration, Withdraw nephrotoxic medication
Proteinuria <1 gr/24 h	Continue ICI	Monitoring
Moderate cases		
sCr 1.5–3 x baseline	Withhold ICI Monitor renal function every 3–7 days	Nephrology consultation +/- start corticotherapy (0.5–1 mg/Kg/24 h)
Proteinuria 1–3.5 gr/24 h	Consider kidney biopsy Withhold ICI if kidney biopsy confirms	Treat the renal pathology diagnosed
Severe cases		
sCr >3 x baseline or > 4 mg/dl	Kidney biopsy Permanent discontinuation of ICIs	Start corticosteroid therapy (1–2 mg/Kg/24 h)
Proteinuria >3.5 gr/24 h	Kidney biopsy Withhold ICI if kidney biopsy confirms	Treat the renal pathology diagnosed
Life-threating cases		
sCr > 6 x baseline or dialysis indicated	Kidney biopsy Permanent discontinuation of ICIs	Intravenous bolus corticosteroid If no response, consider other immunosuppressive agents (MMF, CTX, AZA or infliximab)

AKI, acute kidney injury; MMF, mycophenolate mofetil; CTX, cyclophosphamide; AZA, azathioprine.

corticosteroid treatment, another immunosuppression therapy should be assessed (28). If the deterioration is even greater with an increase of more than 6 times the baseline value or need for KRT, intravenous corticosteroid pulses should be started followed by oral prednisone at 1–2 mg/kg. The use of other immunosuppressants should be considered if improvement has not been observed after 1 week of corticosteroids (28–30).

WHEN SHOULD THE PATIENT WITH AKI AND ICI BE REFERRED TO A NEPHROLOGIST? BIOPSY OR NO BIOPSY AKI IN PATIENTS WITH ICI?

Cancer patients with AKI will benefit from the assessment of a specialist in nephrology who will evaluate the risks and benefits of performing a kidney biopsy (31). There is no scientific evidence regarding the moment of AKI related to ICI referral to a nephrologist, and our suggestions are mainly based on the published guidelines. In brief, if the increase in creatinine is more than 1.5 times the baseline level, consulting a nephrologist is recommended for assessing the need for a kidney biopsy.

One of the important decisions in these patients is when nephrologists should indicate a kidney biopsy, the "gold standard" for kidney disease diagnosis and prognosis. In patients with cancer undergoing treatment with immunotherapy, it is important to identify those who present AKI secondary to acute tubular necrosis with the purpose of avoiding unnecessary treatment with corticosteroids and the temporary discontinuation of immunotherapy. Furthermore, the accurate diagnosis of both interstitial and glomerular kidney pathology will have treatment and prognostic implications.

At present and based on expert opinion and the American Society of Clinical Oncology (ASCO) guidelines (29), kidney biopsy in patients undergoing ICI treatment should be performed if there is proteinuria > 3 g, oliguria, dysmorphic hematuria, and suboptimal response to empirical treatment with corticosteroids (22, 32). However, according to recently published studies, kidney biopsy should be strongly considered if there are several alternatives that justify acute kidney failure (33). In several cases, it is difficult to differentiate AIN from acute tubular necrosis. However, novel urinary cytokine biomarkers that would help to differentiate among them, such as IL-9 and TNF-alpha, are currently under development (34).

However, in cases with severe AKI secondary to ICI with advanced palliative cancer, a kidney biopsy is not mandatory to start corticosteroid therapy. For that reason, strategies for developing biomarkers of AKI associated with ICI may be useful individualizing treatment and diagnosis in the future.

MANAGEMENT OF ICIs IN PATIENTS UNDERGOING DIALYSIS

A high incidence of several types of cancer has been identified in patients undergoing dialysis (35). Additionally, these patients are normally excluded from most clinical trials with cancer therapies, since most of them are aimed to study the pharmacodynamic and pharmacokinetic characteristics of these drugs. In the case of ICIs, these are not modified by the use of dialysis due to their molecular size (36) and do not require dose adjustment. Thus, theoretically, the use of ICI in dialysis patients seems to be safe, although the literature on this topic is scarce (37). Cancer that is most associated with the use of ICI in patients undergoing dialysis is renal carcinoma, followed by genitourinary and melanoma. Nivolumab and pembrolizumab are the two most commonly used drugs (36). Since this population is excluded from clinical trials, evaluating safety in patients undergoing dialysis is a challenge (38). In the previously reported case series, the majority of the adverse events are grades 1 and 2, and the most common adverse effect is hematological, followed by skin and gastrointestinal involvement. A higher frequency of hematological adverse effects has been showed in patients undergoing dialysis than in the general population (39), but the rest of the toxicities have been evidenced less frequently. Published studies that included more than 5 dialysis patients under treatment with ICI, i.e., type of cancer, type of ICI, and outcomes, are summarized in **Table 3** (40–45). As expected, the risk of developing irAEs in patients undergoing dialysis

TABLE 3 | The spectrum of the use of ICI in patients undergoing dialysis.

Studies	Year	Number of patients	More frequent type of cancer	More used type of ICI	Adverse events
Strohbehn et al. (40)	2020	19	Genitourinary	Pembrolizumab and nivolumab	Grades 3–4 myocarditis and pneumonitis
Kuo et al. (41)	2020	11	Urothelial	Pembrolizumab	Grade 3 and 4 anemia
Vitale et al. (42)	2019	8	Renal cell carcinoma	Nivolumab	Grade 3 diarrhea, asthenia and anorexia
Hirsch et al. (43)	2020	8	Urothelial	Pembrolizumab	Dermatitis
Jain et al. (44)	2020	8	Melanoma	Pembrolizumab	Pneumonitis
Tachibana et al. (45)	2019	7	Renal cell carcinoma	Nivolumab	Grade 3 fatigue

ICI, immune checkpoint inhibitor.

seems similar to the general population. A plausible explanation for this is that the excretion of ICIs is not renal, so it is logical that the frequency of adverse reactions is similar in both populations. Management of these immune-mediated toxicities is the same, based on the use of corticosteroids. However, patients undergoing dialysis have many comorbidities, and for that reason, the exposure to corticosteroid therapy must be limited to avoid its adverse effects (46). It is important to highlight that, in dialysis patients who are recipients of a previous kidney transplant, the use of ICI may lead to allograft rejection. The use of mini-pulse steroids can be considered during the first weeks of starting treatment with ICI to prevent allograft intolerance (13, 47). It is worthy to mention that the mortality of dialysis patients with cancer is very high compared with the general population (48). In addition, the incidence of cancer in patients undergoing dialysis is 9.5% higher than in the general population (35, 49). Survival and cancer prognosis in patients undergoing dialysis and immunotherapy is not well known. Therefore, more studies are needed to evaluate the tolerance and the incidence of irAEs derived from ICIs in this population.

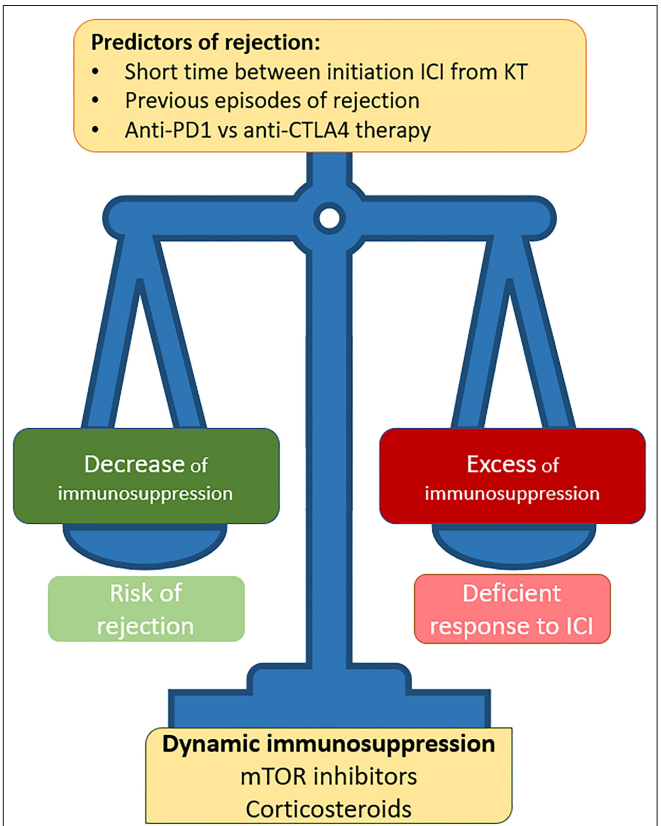

FIGURE 1 | Controversies over the use of ICI therapy in kidney transplant patients.

ICIs IN KIDNEY TRANSPLANTATION

Kidney transplant patients have a 3-fold risk of developing cancer than the general population (50), and it is the second cause of death in this population (51–53). The survival of kidney transplant recipients with cancer is lower than the general population (52). Skin tumors are the most common type of cancer in these patients (54), the use of ICI is highly relevant in this type of cancer, and its treatment with the new targeted therapy has been revolutionized in the past decade (14). Unfortunately, as happens with dialysis patients, kidney graft recipients were usually excluded from most clinical trials with ICIs, and for that reason, there is scarce literature regarding the use of ICIs in this setting. The use of ICI is a challenge in kidney transplant patients for the following two reasons: (1) the use of ICI increases the risk of presenting acute rejection related to the activation of T-type cellular immunity and (2) the use of immunosuppressants can compromise the antitumor activity of immunotherapy (55–57) (**Figure 1**). Thus, it is crucial to individualize the type of ICI used and the immunosuppressive therapy in each case. The risk of rejection increases if the use of ICI is closer to the kidney transplant intervention (55). Anti-CTLA-4 agents appear to have a trend toward a lower risk of rejection compared with anti-PD-1/PD-L1 therapies (58). This may be related to the fact that CTLA-4 plays a fundamental role in the activation of the immune response in the lymph nodes, which has been less frequently associated with rejection; instead, PD-1 and PD-L1 have a key role in the immune activation in the peripheral system (59). In a recently published series, a 40–50% incidence of acute rejection has been described with the use of ICI in transplant patients (13, 14). Usually, the type of rejection

observed is the cellular type without the development of donor-specific antibodies (60); however, Murakami et al. reported in their series of kidney transplant patients with ICI ($n = 69$) that 50% of the rejections were T cell-mediated rejection and the rest were mixed (T cell-mediated and antibody-mediated rejection) (13). The onset of rejection is relatively close to the start of ICI treatment, with a median of 22–24 days (13, 61). In the transplant setting, it is important to differentiate the appearance of rejection and AIN. AIN more frequently presents eosinophilic nodules and an absence of arteritis (8). In addition, the timing from ICI initiation to the development of the renal event differs, with rejection occurring earlier, whereas AIN is usually a later adverse event (61).

Regarding immunosuppression, in kidney transplant patients with cancer, management with mTOR inhibitors is recommended. In addition, it has been shown that the use of mTOR in transplanted patients under treatment with ICI seems to reduce the risk of rejection (13). In addition, patients receiving single-agent prednisone ($\leq$10 mg/day) at CPI initiation seemed to have numerically higher tumor responses to CPI therapy than those receiving single-agent mTOR inhibitors, calcineurin, or combination immunosuppressant therapy regimens (56). The use of "dynamic immunosuppression" has also been described to reduce the risk of acute rejection (47, 62), although the efficacy of this regimen in an ongoing prospective study has yet to be demonstrated (NCT 04339062). Cancer prognosis and overall survival in metastatic diseases have been shown to have better survival in the kidney transplant population treated with ICI than in those who do not receive ICI (13). In melanoma, it has been shown that the use of anti-PD1 in monotherapy in the kidney transplant population has less efficacy than in the general population (63, 64). However, when the combination of anti-PD1 and anti-CTLA-4 is used, response rates are the same as those in the non-transplanted population (65). Taking all together, the use of ICI in kidney transplant patients is an opportunity to improve cancer prognosis in kidney transplant patients; however, individualized management is necessary in terms of immunosuppression, and each case must be approached from a multidisciplinary point of view.

BIOMARKERS OF ICI-INDUCED AIN AND KIDNEY ALLOGRAFT REJECTION

The underlying mechanisms of ICI-AIN are unknown; however, some hypotheses have been postulated as follows: (1) the presence of T cells are reactive against autoantigens expressed in the kidney (66); (2) generation of anti-kidney antibodies (25, 67); (3) cytokine-mediated injury secondary to T-cell activation (68); (4) possibility of preexisting subclinical autoimmune disease (69) and finally (5) loss of tolerance of T cells that had been previously stimulated by other drugs that also induce AIN (58, 70).

Currently, new biomarkers are being developed to early identify renal failure associated with checkpoint inhibitors and their prognoses such as IL 17, sCD163 (soluble receptor expressed from M2 macrophages), IL 6, and blood levels of lactate dehydrogenase (70). Moledina et al., in a prospective study of 218 patients where 15% were diagnosed with AIN, found that urinary levels of tumor necrosis factor-alpha (TNF-alpha) and IL-9 were higher in this group as compared with other biopsied kidney pathologies such as acute tubular necrosis, diabetic nephropathy, or glomerulopathies (34). Another biomarker that can help differentiate interstitial from glomerular pathology is the composition of macrophage subtypes in urine. While the predominance of M1 in urine suggests acute renal failure secondary to AIN, the dominance of M2 in urine could be a source of biomarkers of kidney disease progression, mainly in crescentic glomerulonephritis (71). In cancer patients with renal failure and without the possibility of renal biopsy, it may be difficult to differentiate AIN from acute tubular necrosis, and some urinary cytokines are being studied and developed to facilitate the differential diagnosis, namely, urinary I-TAC/CXCL11, CLXCL10, IL-6, and MCP-1 (72). Finally, Isik et al., in an elegant study of 37 patients where they compared ICI-AKI with non-ICI-AKI, showed that serum C-reactive protein and urine retinol-binding protein/urine creatinine (uRBP/Cr) can be plausible markers to differentiate both types of kidney failure (73).

In the case of kidney transplantation, the histopathological similarity between T cell-mediated rejection and ICI-associated AIN presents a clinical challenge. Recently, interferon alpha-inducible protein 27 (IFI27) gene expression in kidney tissue has been identified as a potential marker to differentiate between both entities (74).

CONCLUSION

The ICI spectrum in kidney disease is wide, from its related immunotoxicity such as AIN and glomerulonephritis to their use in special populations, namely, dialysis and kidney transplant patients. In this review, we highlighted the renal irAEs associated with ICI treatment in patients with advanced cancer. In addition, we also demonstrated that there is an urgent need for randomized clinical trials with ICI involving patients with end-stage kidney disease and kidney transplant recipients. We also addressed some open questions for helping in the daily clinical practice, including when to start corticosteroid therapy in a patient with suspected AKI secondary to ICI, when to refer to the nephrologist or indicate kidney biopsy, the safety of ICI in patients undergoing dialysis, and ICI suggestions in kidney transplant patients.

AUTHOR CONTRIBUTIONS

SB, MB, MR-B, and MS have collaborated on the original idea. SB, MB, and MS wrote the paper. All authors approved the final version of the submitted manuscript.

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Co Treatment With Biologic Agents and Immunotherapy in the Setting of irAEs of Difficult Management

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In recent years, immunotherapy has become an important pillar of cancer treatment, with high response rates regardless of tumor histology or baseline mutations, sometime in patients without any alternative of treatment. Moreover, these treatments are moving from later line therapies to front-line therapies in the metastasic setting. However, immune activation associated with immune check-point inhibitors (ICI) is not selective and a large variety of immune-related adverse events, with an increasing frequency, have been associated with anti-PD1, anti-PD-1/L-1 and anti-CTLA-4 agents. In clinical trials, and sometimes also in real life practice, patients who develop severe toxicities on ICI-based therapies are usually not allowed to resume ICI once their disease progresses, because of the chance of developing severe irAEs on rechallenge with immunotherapies. Moreover, patients with irAEs suffer important side effects due to the high dose corticosteroids that are used to treat them. Therapy with ICI is sometimes the only alternative for certain patients, and for this reason co treatment with classic (DMARDS) or biologic immunosuppression therapy and ICI must be considered. Co-treatment with this type of immunosuppressant drugs, apart from allowing the maintenance of ICI therapy, drive to a lesser use of corticosteroids, with an improvement of the safety and quality of life of the patients. Such a tailored scheme of treatment is mostly an expert opinion based on recommendation and currently there is scarce evidence supporting it. Herein we present comprehensive, current recommendations and real-world data on the use of co-treatment with ICI and DMARDS and biologic immunosuppression.

Keywords: immunotherapy, adverse drugs reaction, immunosuppression therapy, immune check-point inhibitors therapy, autoimmune diseases–therapy

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INTRODUCTION

Immunotherapy has become an important pillar of cancer care, complementing surgery, cytotoxic therapy and radiotherapy in most tumor types. Description of immune-editing by Schreiber (1) as a process that enables escape from immune surveillance to establish overt malignancy and characterization of cancer-immunity cycle by Chen and Mellman (2) impacted on the development of multiple opportunities for therapeutic intervention enhancing tumor immunity. Immune check-point inhibitors (ICI) that target the programmed death protein 1 pathway (anti-PD-1: nivolumab

and pembrolizumab) and its ligand (anti-PD-L1: atezolizumab, avelumab and durvalumab) have obtained the most impacting outcomes with response rates across tumor types of 20–30%. The other group of ICI, anti-cytotoxic T-lymphocyte-associated antigen drugs (anti-CTLA-4: ipilimumab and tremelimumab) engage T cells with inherent capacity for adaptability and memory, that leads to durable responses and long-term survival.

The safety profile of ICI differs from chemotherapy or targeted therapy since immune-related adverse events (irAEs) result from immune activation driving autoimmune manifestations. Overall, the majority of patients treated with ICI developed some irAEs, although the rate of grade 3 events is low (around 10%), except for patients treated with ICI combination. Immune-related adverse events usually present within the first weeks of ICI therapy, though they can occur anytime. In clinical trials, and sometimes also in real life practice, patients who develop severe toxicities on ICI-based therapies are usually not allowed to resume ICI once their disease progresses, because of the chance of developing severe irAEs on rechallenge with immunotherapies. Moreover, patients with irAEs have relevant side effects due to the high dose of corticosteroids that are used to treat them. Not only rapid resolution of irAEs is required, but prevention of irAE recurrence from re-exposure to ICI is also mandatory. Therapy with ICI is sometimes the only alternative for some patients, and therefore co-treatment with classic (DMARDS) or biologic immunosuppression therapy and ICI must be considered. In this way, the use of biologic immunosuppression with cytokine inhibitors usually offers a quicker response in front of DMARDS. Unlike corticosterois and classic DMARDS, which inhibit several inflammatory processes in an unspecific way, cytokine inhibitors provide a targeted clinical approach to reduced ICI-induced inflammation. This fact underlines the need for appropriate therapeutic selection based on a mechanistic understanding of the differential immune conditions that drive the different irAEs (3). Moreover, in the selection of the immunosuppressant agent for a given irAE it is important to take into consideration the current standard treatment for similar non-ICI related conditions. Co-treatment with these types of immunosuppressant drugs, apart from allowing maintenance of ICI therapy leads to a lesser use of corticosteroids and thus, to an improvement in patient safety and quality of life. On the other hand, the co-administration of immunosuppression in the treatment of irAEs has potentially both advantages and disadvantages, given their potential to impact over multiple aspects of the immune system, including infection and antitumour immunity. As an example, there is evidence that an anti-IL 17 antibody, secukinumab, can impair the effect of pembrolizumab in colon rectal cancer (4), or the deleterious effect on the oncological outcome in retrospective studies of DMARDs in patients with immune-related arthritis (5, 6). For all these reasons, at this time a tailored scheme of treatment is mostly an expert opinion based on recommendation, currently with scarce evidence supporting it. Herein we present a comprehensive summary of current recommendations and real-world data on the use of co treatment with ICI and DMARDS/biologic immunosuppression.

SCENARIO FOR CONCURRENT IMMUNOSUPPRESSION AND RATIONALE BASIS

The majority of patients with irAEs will respond to corticosteroids, but a small group of them will require immunosuppressant or biological therapy for corticosteroid dependency or refractoriness. Moreover, in many patients with ICI-induced irAES it might be necessary to maintain immunotherapy, even indefinitely, to achieve or sustain underlying tumor remission. However, the scenario of a patient with moderate to severe irAEs but favorable tumor response to immunotherapy raises doubts about the risk of resuming immunotherapy again. This setting, positioned out of practical guidelines, is complex and depends on multiple factors like subsequent options of oncological treatment, severity and response to treatment of the ICI toxicity and coexistence of other immune-mediated diseases (IMID). Although the final decision in this clinical scenario will depend on the oncologist, it should be endorsed by a panel of different specialist that play a crucial role in establishing a therapeutic strategy in case of resuming immunotherapy. Given the lack of prospective clinical trials, the final decision usually is based on expert opinion and evidence available up to now. In a very interesting recent paper, Haanen (7) propose three possible options of retreatment in case of previous severe toxicity: class switch, rechallenge, and resumption with concurrent immunosuppression.

Regarding the use of ICI with a simultaneous immunosuppression there are limited data available apart from published reports, but it may be the best option for those patients with severe irAEs, mostly in the absence of therapeutic alternatives (7). After a high grade irAEs it is challenging the ICI resumption because of the risk for recurrence and the absence of guidelines. Ideally, the selection of the concurrent agent should be based on the irAE type, response to immunosuppression, life expectancy, quality of life, comorbid conditions and patient preferences.

The basis of theoretical rationale to use cotreatment relies on different relevant arguments. In the first place, there is some evidence that blockade of some endogenous cytokines by monoclonal antibodies can confer anti-tumoral properties. In different clinical situations, second-line immunosuppressant treatment for irAEs frequently includes anti-TNF biological therapy. Some recent evidence shows that blocking TNF alfa, a cytokine with broad well-known pleiotropic effects, before combination therapy with anti-CTLA-4 and anti-PD-1 agents in tumor-bearing mice, would not only prevent autoimmune toxicity but also stimulate anti-tumoral efficacy (8, 9). The underlying mechanism would be the capability of TNF to stimulate activation-induced cell death (AICD) of CD8+ T cells impairing their accumulation in tumors and consequently promoting tumor growth and impeding response to anti-PD-1. This evidence has settled the basis to carry out the TICIMEL study in humans (clinical trials.gov id: NCT03293784), a phase-1b clinical trial in which Nivolumab and Ipilimumab are administered in combination with Infliximab or Certolizumab

(antiTNF antibodies) in patients with advanced melanoma. On the other hand, interleukin-6 can promote tumor progression and metastasis by activation of several oncogenic pathways, increase survival of myeloid derived suppressor cells and inhibition of dendritic cell differentiation (10). Moreover, the IL-6/JAK/STAT3 pathway plays a role in the generation of an inflammatory response that is responsible for many symptoms associated to cancer, like the impairment of the quality of life or the performance status (11). Furthermore, the upregulation of the IL-6 pathway associated with a sustained chronic inflammation may hamper ICI efficacy and worsen the prognosis of the oncologic disease (12). Some reports have linked an increased level of circulating IL-6 with some irAEs like cholangiohepatitis and pneumonitis, and in these settings, the treatment with tocilizumab, a specific IL-6 receptor inhibitor, has been reported effective (13, 14). In the same way, it has demonstrated efficacy in the treatment of cachexia associated with cancer (15).

Additionally, although many immune-related adverse events (irAEs) respond to corticosteroids, a significant number of patients develop corticosteroid dependency or refractoriness. In this subgroup of patients, a corticosteroid-sparing strategy could avoid unnecessary and deleterious side effects. In checkpoint inhibitor-associated colitis there are some factors, like the presence of deep ulcers in the colonic mucosa, that predict those patients at a higher risk of steroid-refractory behavior. In addition, a retrospective study from Abu-Sbeih et al. (16) demonstrates that those patients with ICI–induced colitis who start immunosuppressive therapy earlier ($<$ 10 days after colitis onset vs. $>$10 days) have better outcomes in terms of fewer hospitalizations, a shorter duration of symptoms and less use of corticosteroids.

Another argument to indicate combination therapy in patients with previous irAEs is based on the fact that, in specific advanced tumors, better response rates and survival outcomes were obtained among patients who developed any irAE of any severity as compared to those who did not. Similar results were reproduced by different retrospective analyses both in advanced melanoma and NSCLC (17–19). Another interesting study by Naqash (20) analyzed data from 531 metastatic NSCLC (non-small cell lung cancer) treated with nivolumab after non-response to first line therapy. Thirty-three percent of patients who developed irAE had significantly better outcomes in terms of survival as compared to those who did not develop any irAE. A retrospective analysis from the prospective nationwide Dutch Melanoma Treatment Registry (21) explored the association between severe toxicity development and overall survival. Thousand two hundred fifty patients were included, 25% of whom suffered severe toxicity ($> = 3$), and showed a better survival than those who did not (23 vs. 15 months).

Furthermore, it is also known that immunotherapy discontinuation due to irAE has worse results in terms of survival. Santini et al. (22), in a study with patients with advanced NSCLC treated with anti–PD-L1 who stopped it due to irAEs divided these patients into two groups: those retreated with anti–PD-L1 (retreatment cohort) or those who had treatment stopped (discontinuation cohort). Among those patients with no observed partial responses prior to the irAE, survival outcomes were better in the retreatment cohort. Conversely, for those with objective responses prior to the irAE, survival outcomes were similar in the retreatment and discontinuation cohorts. These results suggest that retreatment, especially in patients with irAEs who had no treatment response prior to irAE onset, could be beneficial in terms of tumor response and survival. However, prospective studies with more patients included would be necessary to validate this data.

REAL WORLD DATA OF CONCURRENT IMMUNOSUPPRESSION

A myriad of case reports of irAEs treated with anti-citokine monoclonal antibodies have been described. Badran et al., (23) described a five-patient case series with different primary tumors who developed gastrointestinal immune-related adverse events, all of them with moderate to severe upper and/or lower gastrointestinal endoscopic lesions. Three out of four developed corticoid-dependency or refractory behavior. All of them received cotreatment with immunotherapy and infliximab over a period ranging from 4 to 10.5 months without tumoral progression or even with improvement in all but one. Regarding GI toxicity, patients remained asymptomatic or with mild symptoms despite ongoing immunotherapy. Another strategy of treatment for immune mediated colitis is the use of vedolizumab, an $\alpha 4\beta 7$ integrin inhibitor that blocks T cells trafficking to the gut, and that is used frequently in the setting of inflammatory bowel disease. Vedolizumab has been used concomitantly when therapy with ICI is restarted after the resolution of immune mediated colitis (16). With this cotreatment, only one out of eight patients presented a recurrence of digestive manifestations.

Another publication from Kim (24) reports three more cases of cotreatment. In one case, a patient who developed an immunomediated arthritis with corticoid dependency and a chronic course, was successfully treated with tocilizumab. The patient remained in complete remission, although immunotherapy was not resumed after receiving tocilizumab. In a second patient, cotreatment with tocilizumab and a non-concrete investigational melanoma therapy for over 15 months, controlled irAE corticodependent arthritis. A third case presented a patient with a non-specified severity colitis and arthritis, treated in combination with ipilimumab and tocilizumab for over 3 months. Both toxicities were kept under remission although with a demonstrated tumor progression. Stroud et al., (25) analyze the use of tocilizumab in a wide variety of irAEs in a single center study. Among the 87 patients who received treatment with nivolumab, 34 (39.1%) required treatment with tocilizumb due to the presence of a wide range of steroid refractory irAEs, including pneumonitis, systemic inflammatory response, cerebritis, hypophysitis, colitis, pancreatitis and hepatitis. Clinical improvement was noted in 79.4% of patients, and in 47% of them more than one dose was required. In a systematic review about the use of tocilizumab, Champochiaro et al. (26), reported that in 85% of the 91 patients in whom this drug was used, a clinical benefit was

observed, without any case of disease progression, and for that reason, the use of tocilizumab may be a safe alternative for long treatments.

While no solid conclusions can be drawn from small series of cases, it generates enough evidence to develop clinical trials and consider cotreatment in specific clinical scenarios.

SAFETY OF CONCURRENT IMMUNOSUPPRESSION

Another aspect of concern when introducing cotreatment therapeutic strategy would be safety issues. Since current recommended strategies do not consider this approach, information can only be gathered from indirect studies. Recent descriptions of the role of TNFα in tumor biology has supported the concurrent immunosuppression with anti-TNF molecules. TNFα produced in the setting of anti-PD-1 blockage leads to an impairment in the CD8+ tumor infiltrating T lymphocyte responses (27). On the other hand, TNFα enhances activation-induced cell death in T cells, that will reduce their viability in the tumor microenvironment (28). For all these reasons by blocking TNFα both studies showed an increase in CD8+ T cell numbers and viability in the tumor microenvironment and draining lymph nodes (28). In this regard, Lesage et al., (29) conducted a retrospective study in order to measure the impact of antiTNF treatment on disease outcome in advanced melanoma patients. Twenty-seven patients with ICI grade 3/4 induced colitis and subsequently treated with antiTNF were included. The overall survival, progression-free survival and objective response rate were compared with those reported in pivotal studies, concluding that neither the occurrence of colitis, nor antiTNF treatment seemed to affect disease outcomes. Weber and colleagues (30) reported GI toxicity occurrence and its management, among patients receiving ipilimumab and nivolumab from two randomized trials. In 22 patients with ICI induced colitis that received steroids along with anti TNF antibodies, there were no differences in tumor response rates and survival as compared to those that received steroids alone. Similarly, Johnson et al., (31) reported no differences in overall survival in 40 patients treated with ICI who developed grade 2–4 colitis and received either high dose steroids or steroids in combination with anti TNF alpha.

A retrospective analysis from the prospective nationwide Dutch Melanoma Treatment Registry (21) explored the association between severe toxicity development and overall survival. Twenty-five percent of the 1,250 patients included suffered severe toxicity ($\geq$3), showing a better overall survival than those who did not (23 vs. 15 months). In contrast to other studies, in this group of patients experiencing severe toxicity, those who received anti-TNF had worse survival outcomes than those receiving corticoids alone. The authors suggest that TNF-alpha blockade would abolish the survival advantage associated with toxicity. Other reasons advocated to explain such discrepancies could be related to different efficacy outcomes measurement and immortal time bias (32).

We should take into account that vedolizumab, due to its mechanism of action by hampering T cell trafficking into the gut, is not recommended in primary gastrointestinal tumors.

Bearing in mind the paucity of solid evidence and clinical experience, cotreatment implies a certain degree of uncertainty. However, in view of the current data available, it seems reasonable to use longstanding cotreatment to prevent flares of irAEs with vedolizumab or adalimumab in ICI-induced enterocolitis, and tocilizumab in ICI-induced inflammatory arthritis.

In view of the uncertainty of the current knowledge, it seems reasonable to undertake prospectively designed studies to assess the relationship of overall outcomes not only with the severity of the irAEs, but also their location, and with the administered treatment.

COEXISTENCE OF AUTOIMMUNE DISEASES

A specific sub-population to take into account when considering cotreatment, are patients with a previous history of autoimmune disease (IMID). These patients have been traditionally excluded from clinical trials so it has been necessary to analyse some retrospective studies to obtain a comprehensive view. Versphol et al., in a single center study involving a large series of patients treated with ICI (33), described that one-third of patients with pre-existing rheumatic disease experienced a disease flare, but in none of them did ICI therapy have to be stopped. Moreoever, no new new rheumatological diseases appeared in these patients. Menzies (34) assessed another cohort of patients with previous history of rheumatoid arthritis, polymyalgia rheumatica, Sjogren's syndrome, thrombocytopaenic purpura, and psoriasis. Twenty-nine percent of them developed irAEs motivating discontinuation of treatment in 8% of them. Another remarkable report (35) explores safety and efficacy of ipilimumab in 30 patients with pre-existing autoimmune disorders. At the time of ipilimumab treatment initiation, 13 patients (43%) were on treatment with at least 1 systemic therapy (6 receiving low-dose steroids, 5 hydroxy-chloroquine sulfate, 1 leflunomide, and 1 methotrexate). Twenty-seven percent of patients had some type of exacerbation of their autoimmune disease that required treatment with 10 patients (33%) experiencing grade 3 to 5 irAEs. A proposed therapeutic strategy in these patients would be to evaluate IMID activity and severity behavior before immunotherapy onset. In a recent study from Abu-Sbeih (36), patients with underlying IBD who needed to be treated with immune checkpoint inhibitors were retrospectively analyzed in order to describe occurrence of irAE. One hundred and two patients were included, 41% of them developed irAE and 21% of them a grade 3–4 colitis. It is also worthy of note that four patients suffered a colonic perforation, 2 of whom required surgery. Regarding therapy, it is noteworthy that 42% of patients were not receiving treatment for the underlying IBD in the 3 months before immunotherapy initiation and that 29% of patients required treatment with infliximab or vedolizumab as part of the treatment for the irAE. Another review with meta-analysis from Meserve (37) draws similar conclusions.

In patients with pre-existing autoimmune conditions it is of paramount importance to diagnose a disease flare in time. Differentiation of an ICI mediated flare of disease and a flare which would have occurred without ICI is sometimes impossible. Afterwards, in the event of an irAEs appearing, combination therapy with anti-cytokine drugs plus immunotherapy could be a treatment option.

DISCUSSION

Cancer immunotherapy has become one of the major breakthroughs in medical evolution that has changed the fight against cancer. However, severe toxicities associated with this type of treatment can sometimes limit its use. Management of severe irAEs can be challenging and most times are based on expert consensus or personal viewpoint due to scarce evidence until now. Co-treatment with anti-cytokine therapy, that is normally used in autoimmune conditions, and ICI has become one of most frequent strategies in the management of irAEs. Cytokine targeted therapies can provide long-term control of irAEs, even with rechallenge of CPI treatment. However, is necessary to conduct prospective investigations on side-effect management of ICI therapy in future advanced-phase trials. Moreover, proper management of severe irAEs requires the intervention of a multidisciplinary team with experience in autoimmune conditions.

The use of immunomodulatory agents in this clinical setting is based not only on the knowledge of the mediators that are involved in the development of these manifestations, mostly TNFα and IL-6, but also on the current standardized treatments of the primary autoimmune conditions that irAEs can mimic. In this review, we take into consideration some of the real word evidence.

In order to synthetize and distill all the above information, it is important to put the focus on the most relevant clinical scenarios that are outside the clinical guidelines. First of all, those patients with moderate to severe toxicity together with a consistent favorable tumor response to immunotherapy, obviously excluding those with life-threating irAE such as myocarditis, pneumonitis, or encephalitis that contraindicate resuming ICI for life. In the second place, those patients with previous IMIDs history. A feasible therapeutic approach in these challenging scenarios could be cotreatment with second-line anti-cytokine immunomodulators depending on the organ affected by the irAE, the predominant type of cytokine involved or the primary autoimmune disease that such irAEs mimic. This new strategy is supported by the evidence that better response rates and survival outcomes have been observed among patients who develop any irAE and that cotreatment with biologic agents does not seem to impair survival or oncological outcomes. However, at this time such recommendation is based only on expert opinion, and for this reason, it is fundamental to carry out prospective studies in order to clarify the best strategy for the management of these challenging manifestations.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Multidisciplinary approach to treatment with immune checkpoint inhibitors in patients with HIV, tuberculosis, or underlying autoimmune diseases

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We reviewed the available information on the use of immune checkpoint inhibitors (ICIs) in populations with special conditions, namely, patients with HIV, tuberculosis, or underlying autoimmune disease. Available data show that treatment with ICIs is safe in patients with HIV; it is advisable, however, that these patients receive adequate antiretroviral therapy and have an undetectable viral load before ICIs are initiated. Tuberculosis reactivation has been reported with the use of ICIs, possibly due to immune dysregulation. Tuberculosis has also been associated with the use of immunosuppressors to treat immune-related adverse events (irAEs). Active tuberculosis must be ruled out in patients with symptoms or signs, and selected patients may benefit from screening for latent tuberculosis infection, although more data are required. Limited data exist regarding the safety of ICIs in patients with cancer and autoimmune disease. Data from observational studies suggest that up to 29% of patients with a preexisting autoimmune disease treated with an ICI present with an autoimmune disease flare, and 30% present with a *de novo* irAE of any type. The frequency of flares appears to differ according to the type of ICI received, with higher rates associated with PD-1/PD-L1 inhibitors. The most common autoimmune diseases for which patients reported flares with ICI therapy are rheumatoid arthritis, other inflammatory arthritis, and psoriasis. Most studies have reported flares or *de novo* irAEs associated with ICIs that were mild to moderate, with low rates of discontinuation and no deaths due to flares. Therefore, the use of ICIs in these patients is possible, but careful monitoring is required.

KEYWORDS

checkpoint inhibition therapy, cancer, human immunodeficiency virus (HIV), tuberculosis, autoimmune diseases

Introduction

Immunotherapy has revolutionized the treatment of cancer, changing the prognosis of several tumor types. Immune checkpoint inhibitors (ICIs) act by blocking immune tolerance pathways such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte antigen 4 (CTLA 4) and helping the immune system to recognize and attack tumor cells; however, cross-reactivity with self-proteins may cause immune-related adverse events (irAEs). irAEs can range from mild to severe or even fatal and can affect any organ system, causing a myriad of symptoms depending on the organ affected. The frequency of occurrence of irAEs differs by the type of ICI used and the characteristics of the patient. For example, treatment with PD1/PDL-1 inhibitors is associated with a lower incidence of irAEs than anti-CTLA-4 antibodies or the combination of agents of both classes (1). It is commonly believed that irAEs result from the autoreactive immune response against non-cancerous cells. To date, most clinical trials have excluded patients with underlying comorbidities such as chronic and opportunistic infections and autoimmune diseases. In patients with human immunodeficiency virus (HIV), there is concern that checkpoint inhibitors may interfere with lymphocyte function and viral suppression. Tuberculosis reactivation has been described in patients under treatment with checkpoint inhibitors, which may be related to the disruption of immune homeostasis. Patients with underlying autoimmune diseases have a higher risk of developing flares after the initiation of ICI treatment. Retrospective data suggest that the incidence of flares in these populations is substantial. Therefore, treatment with ICIs in people with cancer and underlying comorbidities needs to be approached with caution. Patients with chronic and opportunistic infections and autoimmune diseases may be difficult to treat.

In this review, we briefly summarize the current data on ICIs in patients with cancer and underlying comorbidities, specifically HIV infection, tuberculosis, and preexisting autoimmune conditions. We also include key recommendations for the management of these populations. Supplementary Table S1 summarizes the potential complications associated with these three comorbidities and recommendations for managing them.

Immune checkpoint inhibitors in patients with HIV

The life expectancy of patients with HIV receiving antiretroviral therapy (ART) is close to that observed in non-infected people. However, the chronic inflammation status of these patients leads to a higher risk of cancer and other diseases. Specifically, the risk of cancer is estimated to be 69% higher in people living with HIV than in the HIV-negative population (2). The most frequently reported neoplasms in people living with HIV are B-cell non-Hodgkin lymphoma, lung cancer, head and neck squamous cell carcinoma, Kaposi sarcoma, squamous cell skin cancer, classic Hodgkin lymphoma, and hepatocellular carcinoma (3). Cancer in people with HIV usually presents at a younger age and has more aggressive features and poorer outcomes than cancer in the general population (4). Moreover, cancer is one of the leading causes of death among people with HIV (5, 6).

Until recently, people with HIV have been excluded from clinical trials evaluating the safety and efficacy of ICIs in patients with cancer (7). This was due to concerns about the unknown effects of immunotherapy on the T-cell repertoire, the potential exacerbation of immune reconstitution syndrome in patients who recently started ART, pharmacological interactions, the possibility of unmasking opportunistic infections, and the hypothesis that people with HIV may not have sufficient T-cell immunity to benefit from PD-1/PD-L1 blockade (8, 9).

Nevertheless, treatment with ICIs may result in a dual benefit by acting on both the HIV reservoir and the cancer. PD-1-expressing CD4+ T cells constitute a known reservoir of HIV-latent infection; if immune checkpoints play a relevant role in HIV latency, ICIs could potentially improve T-cell responses against HIV antigens (10). Of note, anti-PD-1/PD-L1 treatment is effective in enhancing the production of cytokines such as IFN-γ, TNF-α, and IL-13 in response to HIV antigens (11).

Efficacy and safety of ICIs in patients with HIV

Recently, several clinical trials involving the use of ICIs in people with HIV were reported (12, 13). In a phase 1 study including 6 patients with HIV and no other comorbidities, a single dose of the PD-L1 inhibitor BMS-936559 exhibited a good safety profile, with only grade 1 or 2 adverse events in 3 patients. An increase in HIV-specific CD8+ T cells was observed in 2 patients (12).

Another phase 1 study sought to assess the safety of pembrolizumab in advanced cancer patients with adequately controlled HIV. Thirty patients (6 with Kaposi sarcoma, 5 with non-Hodgkin lymphoma, and 19 with non-AIDS-defining cancer) were enrolled. Grade 1 or 2 irAEs were recorded in 22 patients, and grade 3 irAEs in 6 patients. HIV remained adequately controlled in all patients. As for efficacy, a complete response was observed in 1 patient, partial responses in 2 patients, stable disease in 17 patients, and progressive disease in 8 patients, with 2 patients being not evaluable (13).

A sizeable number of retrospective and prospective cohort analyses, case reports, and literature reviews have suggested acceptable safety and activity of ICIs in people with HIV,

similar to findings in non-infected individuals (9, 14–18). Specifically, the incidence of irAEs does not seem to be increased and virological assessments showed that plasmatic viral load remained suppressed; however, the number of patients included in these studies was small (17).

Recommendations

The Advisory Committee of Spanish Melanoma Group recently reviewed available data and made recommendations for the treatment and monitoring of melanoma patients with HIV who receive ICIs (19), summarized as follows: ICIs should be administered in people with HIV when the HIV viral load is undetectable and in patients receiving ART who have CD4+ T-cell counts ideally above 200 cells per mm^3. Patients with a recent HIV-1 diagnosis should be started on ART before ICI treatment is started; viral suppression is generally achieved 4 weeks after the initiation of ART. In cases in which anticancer treatment cannot be deferred, simultaneous initiation of ICIs and ART could be considered, after assessing risks and benefits.

Before ICI treatment is initiated, screening for latent infections (including viral hepatitis, syphilis, and tuberculosis) should be performed and the infection adequately treated (20, 21). During ICI treatment, the patient should be monitored by an infectious disease specialist, ART should be continued uninterruptedly, and CD4+ cell count and HIV viral load should be periodically monitored. Transitory detectable HIV viral loads below 400 copies/ml (blips) are frequent, have no clinical significance, and require no further action. If the viral load is detected in further consecutive analyses, then additional drug resistance genotypic testing and/or drug monitoring should be performed (15).

It should be noted that the certainty of the evidence upon which these recommendations are based is low and thus the strength of the recommendations is weak. Further randomized controlled trials should confirm these recommendations.

Conclusions

In summary, the evidence suggests that ICIs have a safety and effectivity profile in patients with HIV that is similar to that in the general population. Careful management, including a multidisciplinary approach by a team of oncologists and infectious disease specialists, is advisable.

Immune checkpoint inhibitors in patients with tuberculosis

Tuberculosis is one of the most common infectious diseases worldwide, with about a quarter of the world's population infected with *Mycobacterium tuberculosis*, and it is one of the leading causes of death by an infectious disease. Cancer patients have an increased risk of developing active tuberculosis, and this risk is higher among patients with hematological, head and neck, and lung neoplasms (22, 23).

Although the characteristics of the interaction between the disruption of immune homeostasis caused by ICIs and tuberculosis infection are not fully understood, basic research data suggest that the PD1/PD-L1 pathway may play a substantial role in tuberculosis pathophysiology. Several underlying mechanisms have been described. PD1/PD-L1 deficiency has been associated with an increase in TNF-α, IL-1, and IFNγ (24–26) and dysregulation of the innate immune system, including macrophage and natural killer cell function (27, 28). These data suggest that downregulation of the PD-L1/PD-1 pathway induces an exacerbated inflammatory response that may facilitate the development of symptomatic infection.

In addition, patients treated with ICIs may develop irAEs, for which corticosteroids and TNF-α inhibitors could be prescribed. These therapies, especially TNF-α inhibitors, have been associated with an increased risk of developing active tuberculosis (29, 30).

Effects of ICIs in patients with tuberculosis

Shortly after the introduction of ICIs, cases of tuberculosis reactivation and primary tuberculosis infection following the use of these agents started to be reported (31, 32). Most of the patients in whom tuberculosis was diagnosed received antituberculous treatment, and the course of the infection did not differ, in general terms, from that in patients with tuberculosis and underlying malignancy not treated with ICIs.

Recommendations

There is an urgent need for prospective studies to validate appropriate screening and treatment strategies for ICI-related tuberculosis. Current recommendations for the clinical management of tuberculosis in patients treated with ICIs include the following: screening for latent tuberculosis infection before the initiation of ICIs, managing latent tuberculosis infection in these situations, and diagnosing and treating active tuberculosis in patients receiving ICIs. Here, we provide suggestions for clinical practice based on current evidence and our experience.

Screening for latent tuberculosis infection before initiation of ICIs

Latent tuberculosis infection is a continuous immune response to *Mycobacterium tuberculosis* antigens, but without

evidence of active tuberculosis. Two tests, the tuberculin skin test (TST) and the interferon-gamma release assay (IGRA), are used to screen for latent tuberculosis infection. The IGRA is recommended over the TST for the diagnosis of latent tuberculosis infection in individuals with low-to-intermediate risk of progression to active disease, whereas the IGRA, TST, or dual testing (if the first test is negative) is recommended in patients with a higher risk of developing active tuberculosis (33). The IGRA is frequently favored in developed countries with low disease prevalence because of its more reliable results in patients with previous Bacille Calmette-Guérin vaccination and/or in those receiving corticosteroid treatment.

Before ICIs are initiated, some researchers suggest that an IGRA be performed (31, 34, 35). Varying survival expectancy associated with various types of tumors, differences in the underlying characteristics of patients, risks associated with the cancer itself, and concomitant or previous therapies all undermine the ability to determine the precise risk of developing active tuberculosis associated with ICI therapies (32). A nationwide study in South Korea did not detect increased risk of developing active tuberculosis in patients treated with ICIs compared with the risk in other cancer patients (36). Screening for latent tuberculosis infection is currently not recommended in the general cancer population (22, 23). Therefore, latent tuberculosis infection screening is indicated only in patients with additional risk factors, such as high-risk neoplasms (hematological, head and neck, or lung cancers), other predisposing comorbidities, and/or estimated long survival.

In patients who require anti-TNF-α therapy, the risks and benefits of latent tuberculosis infection screening should be carefully assessed, and different options should be considered. Most guidelines recommend screening because of the significantly increased risk of tuberculosis reactivation in patients receiving these agents for a wide array of inflammatory conditions (30, 37). Screening may also be considered in patients who need high-dose corticosteroids in settings with a high tuberculosis prevalence.

Managing latent tuberculosis infection

Treatment for latent tuberculosis infection should be considered in those with a positive test. The potential harms and benefits of treatment for latent tuberculosis infection need to be weighed on an individual basis, accounting for potential pharmacological interactions, the risk of hepatotoxicity, and expected survival. An assessment with an infectious disease specialist and clinical monitoring during treatment are advisable. It is generally accepted that initiation of ICIs should be delayed about 2 weeks after the initiation of antituberculous treatment, in order to improve tolerance and minimize the possibility of immune reconstitution symptoms (32).

Diagnosing and treating active tuberculosis in patients receiving ICIs

Active tuberculosis may develop in a patient receiving ICIs. Diagnosis may be complicated by the lack of specificity of signs and/or symptoms, which may mimic oncological disease progression or pseudoprogression, bacterial or fungal infection, or pulmonary irAEs. Therefore, high clinical suspicion is key to an accurate diagnosis. Microbiological confirmation through invasive or non-invasive samples is paramount and necessary in guiding adequate antimycobacterial therapy, which must be weighed according to the characteristics of the patient and potential pharmacological interactions and toxicities. Liver inflammation in the course of treatment must also be carefully assessed, since it may represent toxicity caused by antituberculous therapy or an irAE or be associated with the underlying disease. It is generally supported that ICIs should be withheld during active infection for 2–4 weeks because of the possibility of an exaggerated inflammatory response (32).

Conclusions

In conclusion, although the use of ICIs has been linked to the development of tuberculosis, the precise risk of this association has not been established. Current evidence does not clearly support routine latent tuberculosis infection screening in these patients. Treatment for latent tuberculosis infection or active tuberculosis should be individually evaluated.

Immune checkpoint inhibitors in patients with underlying autoimmune diseases

About 3–5% of the world's population has an autoimmune disorder (38–41). Autoimmune and chronic inflammatory diseases have been significantly associated with increased risk of cancer (42). Between 10 and 30% of patients with cancer have one of the more than 80 different autoimmune diseases, either localized in an individual organ or with a systemic presentation. Patients with cancer and autoimmune diseases have shorter survival durations, poorer quality of life, and higher health care costs than do cancer patients without autoimmune diseases (43–45).

Cancer patients with autoimmune diseases have been excluded from most ICI trials because of concerns about increasing their risk of irAEs and/or flares of their concomitant autoimmune disease. The exact pathophysiology of irAEs is not known and may vary across toxicity phenotypes, but it is attributed to the expansive upregulation of immune pathways caused by ICIs, resulting in inflammatory and autoimmune manifestations that can affect almost any system or organ and can be severe. Although numerous reports have been published

describing the occurrence of irAEs and flares in patients with autoimmune diseases ["who are treated with ICIs for cancer"?], most are retrospective in nature. To date, no controlled trial data exist regarding the safety and efficacy of ICIs in patients with cancer and autoimmune disease. Here, we review the evidence of relevant observational data to provide a comprehensive summary of the occurrence of irAEs and autoimmune disease flares and of cancer response to ICIs in patients with preexisting autoimmune disease. Data are still needed on the incidence of irAEs in patients with active vs. stable autoimmune disease and on the use of DMARDs (disease-modifying antirheumatic drugs)/steroids at the initiation of ICI therapy and per ICI used (anti-PD1, antiPDL1, anti-CTLA4).

Occurrence of irAEs and flares in patients with preexisting autoimmune diseases

Previously, a review of 123 patients whose cases were described in 49 publications reported that in 92 (75%) of these cases, there was an exacerbation of autoimmune disease, irAEs, or both with ICI treatment. The large majority of patients in the review had melanoma (46). However, pooled data from 11 case series (47–57) suggested that the number of patients experiencing any type of irAEs (flares or *de novo*) was 55% [95% confidence interval (CI), 44–66%] (58). For flares, the pooled frequency was 29% (95% CI, 11–49%) and for *de novo* irAEs it was 30% (95% CI, 24–35%). When categorized by type of ICI, 37% (95% CI, 25–50%) of the patients who received anti-PD-1/PD-L1 agents had autoimmune flares, compared with 29% (95% CI, 11–49%) who received anti-CTLA4. Flares were more commonly reported in patients with arthritis (rheumatoid, chronic unspecified, or inflammatory) (33%) and psoriasis (20%).

Risk of irAEs in patients with and without autoimmune disease

Although evidence from a report in 2017 (47) suggested that the risk of developing an irAE over 2 years of follow-up after initiation of ICIs in patients with autoimmune diseases was 1.5 times higher than that in patients without an autoimmune disease (95% CI, 1.1–2.2), another study in 2019 (59) reported no statistically significant increase in the risk of grade 3 or 4 irAEs, suggesting that the increased risk observed may be limited to grade 1 or 2 toxicities. A similar risk of developing any type of irAE was reported for patients with autoimmune diseases when compared with patients without autoimmune disease who had developed an irAE after exposure to ipilimumab (47).

One study compared the flare rates in patients with autoimmune rheumatologic diseases to rates in patients with autoimmune non-rheumatologic diseases. Patients who had a rheumatologic disease were 4.1 times more likely to develop a flare (95% CI, 1.3–13.4) (56). However, for patients with stable autoimmune disease at the start of ICI therapy, the flare rates were lower (18%) than those of patients with uncontrolled disease (50%) (55).

Cancer response to ICI in patients with cancer and preexisting autoimmune diseases

The presence of preexisting autoimmune disease was not associated with cancer outcomes such as progression-free survival and overall survival in a systematic review of observational studies (47–49, 52–55, 57, 58). The pooled proportion of patients with cancer and autoimmune disease with complete response after treatment with any ICI was 6% (95% CI, 0–18%) (47–58). The pooled proportion of patients with partial response was 25% (95% CI, 15–36%), with stable disease was 21% (95% CI, 10–34%), and with progressive disease was 46% (95% CI, 31–61%) (58).

The pooled frequency of permanent discontinuation of the ICI was 12% (95% CI, 4–24%) and of temporary discontinuation was 9% (95% CI, 2–18%) (58). Pooled mortality was 31% (95% CI, 11–56%), although none of the deaths were related to the autoimmune disease (47, 49, 52, 53, 55, 56, 58). Death rates were lower in patients with autoimmune disease who developed a flare compared with those with no flares (58).

Recommendations

The European Society of Medical Oncology has proposed a two-step approach for the care of patients with cancer and underlying autoimmune disease who are considering ICIs. The first step consists of a short-term prevention strategy in which non-immunosuppressant agents are discontinued and replaced with a first-line immunosuppressive or more targeted treatments as opposed to systemic immunosuppression. It is preferable that the autoimmune disease be controlled for 2–4 weeks before ICIs are started. For patients with a rapid disease course, immunosuppressants and ICIs can be introduced simultaneously. Once therapy with ICIs has commenced, close monitoring to manage any potential flares is imperative. Finally, the guidelines recommend maintaining immunosuppressants for the duration of ICI therapy to avoid severe flares (60). In addition, the National Comprehensive Cancer Network recommends the involvement of a multidisciplinary team that includes an autoimmune disease specialist in the decision to initiate ICIs and, when possible, the avoidance of combination therapy with PD1/PD-L1 and CTLA-4 agents (61).

Conclusions

In conclusion, immune checkpoint inhibition in patients with known autoimmune diseases is possible but requires careful monitoring. Several studies across the globe have reported the use of ICIs in patients with cancer and autoimmune disease in whom the rates of flares and *de novo* irAEs were substantial. Partial response is achieved by at least a quarter of patients with advanced-stage cancer, and permanent discontinuation of the ICI is needed in only a few patients with cancer and autoimmune disease. Therefore, the risk-benefit ratios of immunotherapy in patients with preexisting autoimmune diseases need to be carefully discussed with patients.

Author contributions

JA-C, ML-O, and IR-C contributed equally to the conception and design of the article, divided the sections, were responsible for one of the three sections, revised and interpreted critically the relevant literature for her/his section and drafted it, and finally reviewed the complete final manuscript. All authors contributed to the article and approved the submitted version.

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Supplementary material

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The Low Incidence of Viral Hepatitis Reactivation Among Subjects on Immunotherapy Reduces the Impact of Suboptimal Screening Rate

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Background and Aims: Immunotherapy with immune checkpoint inhibitors (ICIs) is a pillar of many advanced tumors. However, there is scarce data concerning the rate of viral hepatitis screening in this population or the risk of viral reactivation.

Methods: Retrospective–prospective study that includes all patients who began ICIs between January/2019 and December/2020 in a University Hospital. Data on viral hepatitis screening prior to the beginning of ICIs were collected. In subjects lacking information, serological tests were requested prospectively. Among HBsAg, anti-HBc, or anti-HCV positive subjects, reactivation was prospectively assessed.

Results: During the 2-year period of study, 595 subjects received ICIs (61.2% male, mean age 63 years). The most prevalent cancers found were 35.5% lung cancer, 12.1% melanoma, and 8.2% head and neck; ICIs schemes were mainly anti-PD1 (65.7%), followed by anti-PD-L1 (19.2%), and combined therapy (13.6%). Prior to immunotherapy, anti-HCV screening was performed in 462 (77.6%) subjects, HBsAg in 462 (77.6%), anti-HBc in 335 (56.3%), and the complete screening in 328 (55.1%). The anti-HBc screening was more frequently ordered among patients treated with concomitant systemic therapy ($p = 0.003$), especially in the case of chemotherapy ($p = 0.015$), though HCV screening was more commonly performed in concomitant therapies different from chemotherapy ($p = 0.001$). Serological tests were completed prospectively in those alive, leading to an overall prevalence for anti-HCV of 3.5%, HBsAg at 1.3%, and anti-HBc of 15.2%. HCV-RNA was detected in 2/19 (both patients with hepatocellular carcinoma), HBV-DNA in 4/7 HBsAg positive, and in 1/75 anti-HBc positive subject. Five out of the 7 HBsAg carriers and 1/75 anti-HBc+ subjects (due to concomitant antiretroviral therapy) received antiviral prophylaxis. Neither cases of HBV reactivation nor changes in HCV viral load were observed.

Discussion: HBV and HCV screening prior to immunotherapy is suboptimal. Though the rate of viral hepatitis reactivation seems extremely low, efforts should be made to optimize viral hepatitis screening prior to immunotherapy for the selection of candidates for either antiviral prophylaxis or periodical follow-up.

Keywords: immunotherapy, checkpoint inhibitors, viral hepatitis, screening, hepatitis B, hepatitis C, cancer, oncology

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have become a breakthrough in the treatment of many advanced cancers. Immunotherapy with ICIs is based on the use of monoclonal antibodies that target checkpoint molecules, promoting the activation of the immune system and inducing the elimination of metastatic cells (1). The most commonly used mechanisms are cytotoxic T-lymphocyte-associated molecule-4 (anti-CTLA-4), programmed cell death receptor-1 (anti-PD-1), programmed cell death ligand-1 (anti-PD-L1), and anti-LAG3. To date, immunotherapy with ICIs has been approved for more than 17 different cancer types and growing (2).

It is well-known that there is a risk of hepatitis B virus (HBV) reactivation associated with chemotherapy, especially in the hematology setting. Furthermore, chronic hepatitis C is more prevalent in subjects with some solid-organ tumors such as hepatocellular carcinoma but also non-Hodgkin's lymphoma (3). Yet, screening of viral hepatitis is not universal among candidates for chemotherapy, a fact that has led to the development of electronic alerts and platforms for the promotion of diagnosis among physicians prescribing chemotherapy (4). These actions have been based on the poorer prognosis in terms of both morbidity and mortality among patients with HBV reactivation (5, 6). Unlike chemotherapy, data on the effect of immunotherapy on viral hepatitis is scarce and information about the awareness of this topic among ICI-prescribing physicians is lacking. In most registry studies of ICIs, individuals with underlying viral hepatitis were excluded or at least needed to be on nucleos(t)ide analog (NAs) in the case of patients with chronic HBV, to be included. Retrospective studies from real-world cohorts have shown that up to 17% of HBV-infected subjects may suffer from reactivation in cases of immunotherapy without antiviral prophylaxis (7). With regard to resolved HBV infection (isolated anti-HBc+ subjects), few cases of reactivation have been reported so far (8, 9), though data on the real incidence of reactivation remains unknown (10). In contrast to HBV, HCV viral load seems to be unaltered or even reduced by the effect of ICIs (11).

The aim of this study was to analyze the rate of testing for hepatitis B and C before starting ICIs as a way to assess the awareness of Oncologists about viral hepatitis in the population on immunotherapy. In addition, we prospectively estimated the prevalence of viral hepatitis in patients undergoing immunotherapy and the potential risk of viral hepatitis reactivation in this setting.

PATIENTS AND METHODS

Study Design

This is a retrospective–prospective study that included all patients who began oncological immunotherapy between January 2019 and December 2020 at Vall d'Hebrón University Hospital (Barcelona, Spain). Through the electronic records of the Pharmacy Department of our hospital, all patients who began Oncological immunotherapy within the period of study were selected. Data on viral hepatitis screening prior to the beginning of ICIs and demographic characteristics were collected retrospectively. In subjects lacking information and alive at the time of the study (April to December 2021), serological tests were requested prospectively.

This study was approved by the Vall d'Hebron Hospital ethics committee and was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements.

Data Collection

Data collected retrospectively included patients' demographic characteristics: sex, age, tumor localization, type and date of diagnosis, evidence of prior liver disease, or presence of liver metastases. Regarding therapy, the parameters collected were: previous oncologic treatments (chemotherapy, immunotherapy); current treatment, defined as immunotherapy anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-LAG-3; ICIs discontinuation and reason for discontinuation; concomitant systemic drugs (e.g., chemotherapy or anti-angiogenic drugs), concomitant corticoids. Viral hepatitis screening prior to ICIs consisted of antibodies to hepatitis C virus (anti-HCV), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and surface antigen antibodies (anti-HBs). *Complete viral hepatitis testing* included anti-HCV, anti-HBc, and HBsAg performance. Screening for the human immunodeficiency virus (HIV) was also recorded.

It was also recorded in anti-HCV, HBsAg, or anti-HBc positive subjects whether HCV-RNA or HBV-DNA was carried out. Information on concomitant NAs during ICIs was also gathered, as was the reason for the prescription (HIV infection; antiviral prophylaxis). The last update of data was in February 2022.

In subjects lacking viral hepatitis screening and alive at the time of the study, a blood test including HBsAg, anti-HCV, and anti-HBc was prospectively requested for those still on immunotherapy. In subjects positive for either anti-HCV or anti-HBc, HCV-RNA and HBV-DNA were carried out every 6 months to rule out viral reactivation.

Outcomes

The primary aim of the study was to assess the rate of HBV (HBsAg and anti-HBc) and HCV (anti-HCV) screening prior to immunotherapy as a measure of the Oncologists' awareness of the risk of viral hepatitis reactivation among subjects undergoing ICIs. The secondary endpoint was the assessment of viral reactivation associated with immunotherapy among individuals with viral hepatitis infection: resolved hepatitis C (anti-HCV+/undetectable RNA), active hepatitis C (anti-HCV+/detectable RNA), chronic HBV infection (HBsAg+), past HBV (anti-HBc+). HBV reactivation was defined by the reappearance or rise in HBV-DNA above baseline in patients with chronic hepatitis B, or the appearance of HBV-DNA in the blood or reverse seroconversion to positive HBsAg in those with past HBV infection (isolated anti-HBc+), regardless of the presence of ALT increase (12–14). HCV reactivation was defined as a 2-log increase in HCV-RNA levels compared to baseline. Screening for HIV prior to the beginning of ICIs was also recorded to compare the degree of awareness between viral hepatitis and HIV infection.

Methods

Serological markers for HBV (HBsAg, anti-HBc, and anti-HBs), HCV, and HIV were analyzed by commercially available electrochemiluminescence immunoassays (COBAS 8,000, Roche Diagnostics, Rotkreuz, Switzerland). Serum viral loads were quantified by an automated real-time PCR COBAS 6,800 (Roche Diagnostics, Mannheim, Germany): HBV-DNA (COBAS HBV test- lower limit of quantification of 20 IU/mL and lower limit of detection-LLD of 10 IU/mL) and HCV-RNA (COBAS HCV test; LLD of 15 IU/mL).

Statistical Analysis

Normally distributed quantitative variables were expressed as mean and standard deviation (SD) and non-normally distributed as the median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages and compared using the chi-square or Fisher exact test, as appropriate. The results were considered statistically significant when the *p*-value was below 0.05. All statistical analyses were performed using IBM SPSS, version 26.0 (SPSS Inc, Armonk, NY, USA).

RESULTS

Baseline Characteristics of Patients

During the 2-year period of study, 595 individuals received ICIs. The majority were male (61.2%), with a median age of 64 years. Forty-three (7.2%) subjects had a history of liver disease, mainly alcohol, and metabolically associated fatty liver disease, though only 15 (2.5%) presented signs of liver cirrhosis. The main characteristics of patients are summarized in **Table 1**. The most prevalent tumors were lung cancer, melanoma, head and neck, and colorectal which account for up to 60% of cancers, as shown in **Figure 1A**. Approximately half of the cohort (53.2%) had been previously treated with chemotherapy, and up to 15% had already received a prior line of therapy including ICIs.

TABLE 1 | Main characteristics of patients treated with immune checkpoint inhibitors ($N = 595$).

Patients' characteristics	
Male gender	364 (61.2%)
Age (years)	64 (57-72)
Race	
Caucasian	582 (97.8%)
African/Hispanic/Asian	4 (0.7%)/8 (1.3%)/1 (0.2%)
Underlying liver disease	43 (7.2%)
Underlying liver cirrhosis	15 (2.5%)
Liver metastasis	123 (20.7%)
Previous oncological therapy	
Previous chemotherapy	316 (53.2%)
Previous immunotherapy	90 (15.2%)
Current immunotherapy	
Combined systemic therapy (all)	194 (32.6%)
Chemotherapy	104 (17.5%)
Tyrosine kinase inhibitor	21 (3.5%)
IL-2 agonist	14 (2.4%)
VEGF inhibitors	14 (2.4%)
Inducible Co-Stimulator (ICOS)	12 (2.0%)
MET inhibitors	8 (1.3%)
PARP inhibitors	7(1.2%)
Corticoids at the beginning of ICIs	11 (1.8%)

Factors are expressed as n (%) or median (IQR).

The current scheme of immunotherapy is summarized in **Figure 1B**. The vast majority (84.9%) of individuals received monotherapy with either an anti-PD1 or anti-PD-L1 and 13.6% a combination of anti-PD-1 and anti-CTLA-4 agents. Concomitant systemic therapy was given to 194 (32.6%) subjects, with chemotherapy the most common (104, 17.5%), followed by tyrosine-kinase inhibitors (21, 3.5%) (Complete list in **Supplementary Table 1**). Twenty-three (3.9%) subjects had received corticoids in the past. Overall, 73 (12.3%) patients from the cohort received corticoids, either at the beginning (11, 1.8%) or during the course of immunotherapy. Median duration of immunotherapy at the time of the study was 9.4 months (range 1–86.3).

Viral Hepatitis Screening Prior to Immunotherapy

The percentage of patients with viral hepatitis screening previous to ICIs is summarized in **Figure 2A**. Overall, 328 (55.1%), subjects had *complete viral hepatitis testing* prior to ICIs, a percentage lower than the 392 (65.9%) subjects screened for HIV ($p < 0.001$). The percentage of subjects with ordered *complete viral hepatitis testing* prior to ICIs was higher among those with HIV results (67.1 vs. 32.0%, $p < 0.001$). Likewise, data on *complete viral hepatitis* was more frequent in patients who had been previously treated with either chemotherapy (59.6 vs. 50.0%, $p = 0.012$) or immunotherapy (72.2 vs. 52.1%, $p < 0.001$).

Viral hepatitis screening differed in relation to the type of concomitant medications. The anti-HCV request was higher

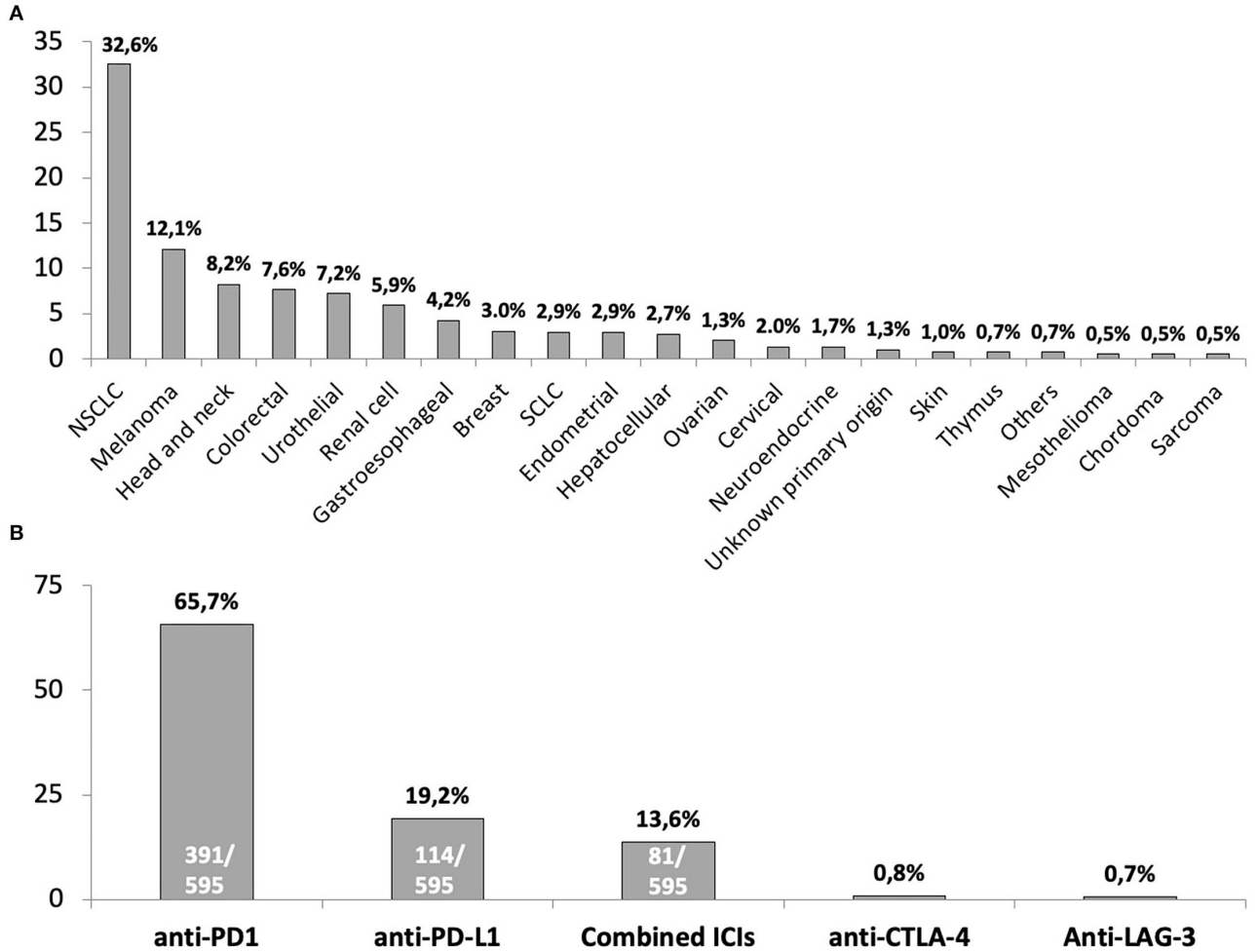

FIGURE 1 | Summary of underlying cancers for immune checkpoint inhibitors therapy **(A)** and immune checkpoint inhibitors scheme prescribed to included patients **(B)**. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer. The four (0.7%) subjects included in the "*Others*" tumors category comprised: 1 paraganglioma, 1 solitary fibrous tumor, 1 thyroid, 1 Hodgkin Lymphoma. In the case of monotherapy with anti-CTLA-4 or anti-LAG-3, the absolute number of subjects who received these schemes of ICIs were 5 and 4, respectively.

in subjects undergoing combined therapy ($p = 0.018$), mainly due to the greater awareness among those of systemic therapies different from chemotherapy (90.2 vs. 76.2%, $p = 0.001$) as shown in **Figure 3A**. These findings were also observed in the case of HBsAg, with a tendency to higher screening rates in individuals on *other* concomitant therapies (85.3 vs. 77.5%, $p = 0.053$) (**Figure 3B**). However, in the case of anti-HBc, the rate of screening was higher among individuals receiving concomitant chemotherapy ($p = 0.015$) and globally among those on combined systemic therapy ($p = 0.003$) as shown in **Figure 3C**. No differences were observed in the rate of viral hepatitis screening in the cohort of 26 individuals with current or previous therapy with corticoids (anti-HCV: $p = 0.543$, HBsAg: $p = 0.543$, anti-HBc: $p = 0.227$, *complete viral hepatitis testing:* $p = 0.192$).

Prevalence of Viral Hepatitis Among Subjects Undergoing Immunotherapy

The prospective screening of those individuals without previous data and still alive at the time of the study revealed an overall prevalence of hepatitis markers of 3.5% for anti-HCV, 1.3% for HBsAg, and 15.2% for isolated anti-HBc (**Figure 2B**). This prospective search allowed the identification of two unknown cases of HCV infection and 28 isolated anti-HBc-positive subjects. No additional cases of HBsAg were detected.

Concerning hepatitis C, viral load was requested by the treating physician in 16 (84.2%) cases. In the remaining anti-HCV cases it was performed later and linked to the present study. All except 2 (11.5%) out of the 17 anti-HCV positive subjects had undetectable HCV-RNA, largely due to previous antiviral therapy. The two individuals with detectable HCV-RNA

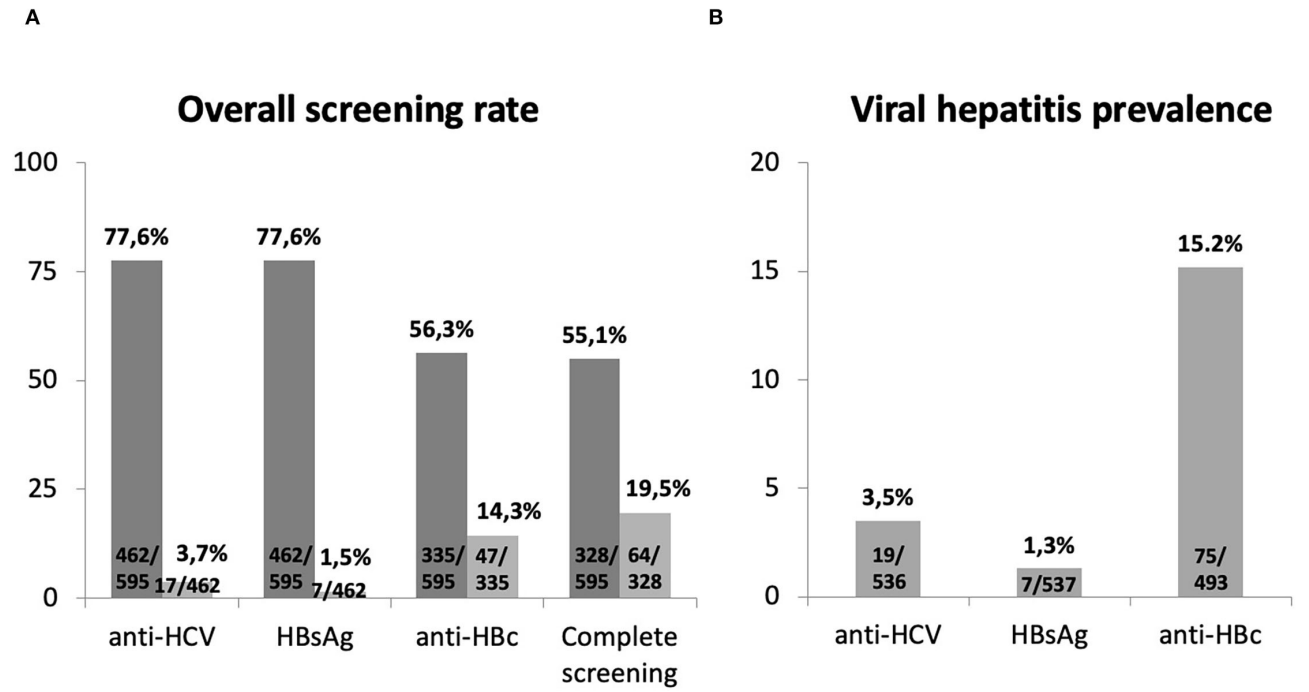

FIGURE 2 | (A) Rate of viral hepatitis markers ordered prior to the beginning of ICIs (dark gray) and the results from these tests (light gray). **(B)** Overall viral hepatitis prevalence after the prospective request of viral hepatitis markers in alive patients on ICIs. *Complete viral hepatitis testing* refers to the combination of HBsAg, anti-HBc, and anti-HCV.

presented hepatocellular carcinoma. Among the seven HBsAg-positive patients, HBV DNA was tested in 6 (85.7%) prior to the start of immunotherapy and it was detectable in five cases. Among the 75 isolated anti-HBc-positive individuals HBV-DNA was requested in only 26 (34.7%) and just one patient presented a detectable viral load (28 IU/mL).

Viral Hepatitis Reactivation

No cases of HCV reactivation were detected. Antiviral therapy were not initiated in the two patients with detectable HCV-RNA during immunotherapy and no changes in HCV-RNA levels were observed. Likewise, HCV-RNA remained undetectable in all subjects with prior resolved hepatitis C during a median 8-month ICIs therapy (range, 2–35).

HBV reactivation was not observed in any of the 7 HBsAg-positive cases. Five (71.4%) received antiviral prophylaxis during ICIs therapy. Four of these five subjects presented detectable HBV-DNA at baseline (median value of 104 IU/mL; range 0–11,475 IU/mL). In all patients on antiviral prophylaxis, HBV-DNA became and remained undetectable during ICIs therapy. In the 2 subjects who did not receive antiviral prophylaxis, baseline HBV-DNA values were 12.000 and 11.300 IU/mL, respectively. One of these patients died 2.7 months after the beginning of immunotherapy due to cancer progression and no HBV-DNA determination was available within this time. The other case completed 17 cycles of an anti-PD1 agent, but no viral load was determined during the course of ICIs despite the fact that the patient presented increased ALT levels throughout immunotherapy. HBV-DNA after ICIs discontinuation was 2,450 IU/mL.

HBV reactivation was not detected in 61 out of 75 anti-HBc-positive individuals who had periodical determinations of HBsAg and HBV-DNA during a median ICI therapy of 11 months. None of them received antiviral prophylaxis except for an HIV co-infected patient who underwent a Tenofovir-containing antiretroviral regimen. The only patient with a baseline detectable HBV-DNA remained similar throughout immunotherapy despite the lack of antiviral prophylaxis (last HBV-DNA value 20 IU/mL).

DISCUSSION

Herein we present novel results on the rate of screening of Oncologists for the risk of viral hepatitis associated with immunotherapy, with just 55.1% of patients having complete screening prior to ICIs. Moreover, we provide prospective data on the risk of HBV reactivation in a cohort of 61 subjects with past HBV infection (isolated anti-HBc+), with no cases meeting the criteria for reactivation during a median follow-up of 11 months of ICIs. To our knowledge, this is the first work focusing on the rate of viral hepatitis tests performed prior to immunotherapy, a useful tool to assess the awareness of ICIs' prescribers of the potential risk of immunotherapy on patients with chronic viral liver diseases.

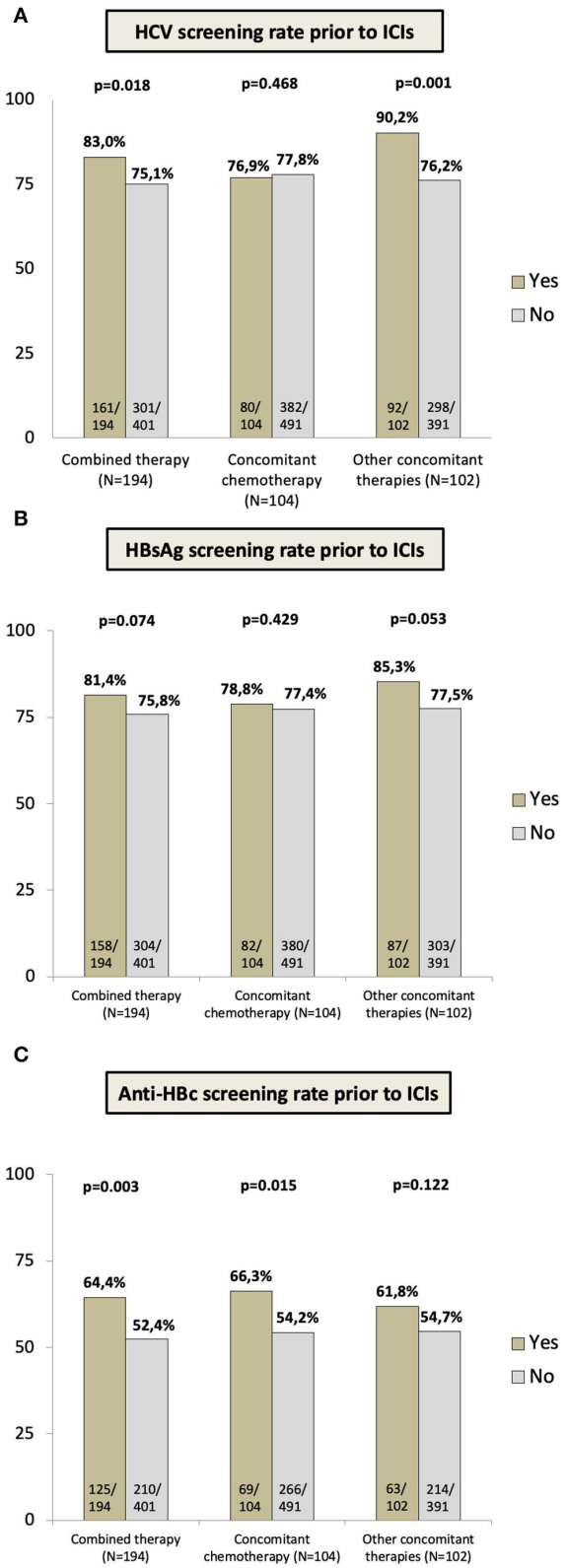

FIGURE 3 | Rate of viral hepatitis testing ordered previous to ICIs starts according to the prescription of concomitant medication (All combined therapy; concomitant chemotherapy; concomitant systemic therapy different

(Continued)

FIGURE 3 | from chemotherapy mainly tyrosine-kinase inhibitors, IL-2 agonist, inducible co-stimulators-ICOS and anti-VEGF drugs as summarized in **Supplementary Table 1**: **(A)** hepatitis C virus screening prior to ICIs. **(B)** HBsAg screening prior to ICIs. **(C)** anti-HBc screening prior to ICIs.

This issue has been widely explored and discussed in the setting of chemotherapy, especially in those schemes including rituximab, an anti-CD20 agent. The high rates of HBV reactivation in patients on rituximab-containing chemotherapies led to the Food and Drug Administration and European Medicines Agency recommendations of HBsAg and anti-HBc screening prior to immunosuppression, to identify individuals with criteria for antiviral prophylaxis to avoid reactivation. As reported by the Anderson Center (USA), these guidelines had a huge impact in the hematology setting, with a rate of screening of over 70% among individuals with hematologic malignancies (15). However, the percentage of tests among patients with solid-organ tumors remained very low (10%) despite these recommendations (15). Data from our area produced similar results, with 60.5% of hematological patients with complete viral hepatitis tests ordered prior to chemotherapy, a percentage that rose to roughly 88% when an electronic-alert system was set up (16).

In comparison to standard chemotherapy, data on the risk of HBV reactivation in the setting of oncological immunotherapy is scarce, since all patients in the registry study of the ICIs were on NAs. Furthermore, given the mechanism of action of the ICIs, these drugs may play a role in the treatment of chronic hepatitis B. For instance, the efficacy of nivolumab, an anti-PD1 agent, has been tested in HBV virological-suppressed patients, though the reported impact on HBsAg levels after a single dose was modest (17). The exponential use of immunotherapy in clinical practice led to the emergence of isolated clinical cases reporting HBV reactivations in patients undergoing ICIs (8, 18). Retrospective data from 114-HBsAg+ individuals from China revealed a 17.2% rate of HBV reactivation among those treated with anti-PD1 agents in case of the absence of concomitant antiviral prophylaxis (7). More recently, a retrospective cohort including 511 HBsAg-positive subjects revealed HBV reactivation rates of 0.4 and 6.4% in those with and without antiviral prophylaxis, respectively, emphasizing the importance of HBV prophylaxis (19).

To date, experience on the possible impact of ICIs on individuals with resolved HBV infection has scarcely been explored. In this regard, Shah and Kothapalli reported no changes in HBV viral load among eight and five anti-HBc+ subjects treated with ICIs without antiviral prophylaxis (20, 21). These preliminary results are in line with ours, where no cases of HBV reactivation were observed among the 61 anti-HBc+ individuals with prospective data on HBV markers. For the time being, the current evidence on the extremely low risk of HBV reactivation among subjects with resolved HBV infection recommends against the use of antiviral prophylaxis in the case of therapy with ICIs.

Regarding HCV, despite the high percentage of cure achieved by the direct-acting antivirals (DAA) therapy and the efforts of micro and macro elimination programs for diagnosis and linkage to care of HCV-infected individuals, published data on

screening among solid-organ cancer subjects on chemotherapy revealed a rate as low as 14% (22). In our cohort, 3.5% of patients were anti-HCV positive, a prevalence higher than that reported among the general population in our setting (23), probably due to the inclusion of individuals with high-risk factors for HCV exposure, such as those with hepatocellular carcinoma, head and neck, and lung cancer. As reported with HBV, literature on ICIs and chronic hepatitis C is also limited. In our cohort, just two patients presented active HCV infection, with the rest showing undetectable viral load, the majority after the achievement of sustained virological response through DAAs. No changes in HCV-RNA were observed in the two patients with detectable viremia at the beginning of ICIs, neither was there a relapse of HCV in patients with baseline undetectable HCV-RNA. This observation is in line with preliminary results from both anti-PD1 and anti-CTLA-4 agents, where even some transient reductions in HCV RNA were reported (11, 24). More recently, in a matched cohort study of nivolumab, an anti-PD1 agent, for renal cell carcinoma, no impact on HCV-RNA was described in 14 individuals with HCV infection (25).

Our study has some limitations. This is a retrospective and single-hospital-based study and therefore data on some patients were missed. However, we report novel and interesting results on the degree of awareness of Oncologists about the risk of prescribing ICIs for patients with viral hepatitis according to the rate of pre-treatment ordered screening. Furthermore, the prospective gathering of tests in patients with a lack of results resulted in data on the prevalence of the viral hepatitis marker among patients undergoing oncological immunotherapy and the risk of HBV reactivation in this population.

In summary, herein we report novel results on the screening of viral hepatitis among immunotherapy prescribers, revealing that HBV and HCV screening prior to ICIs start is suboptimal. Though the rate of viral hepatitis reactivation in this population seems extremely low, efforts should be made to optimize viral hepatitis screening prior to immunotherapy for the selection of candidates for either antiviral prophylaxis or periodical check-up.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Vall d'Hebron Hospital Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LA, JB, and LR-O contributed equally to this work by collecting the data and helping write the manuscript. MR-B guided the data collecting, performed the statistical analysis, and wrote the manuscript. AB-D, AC-P, EM-C, CO-V, ND-M, MC, and AF helped to discuss the results. MB supervised the final manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.916213/full#supplementary-material

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Incidence and characteristics of adverse drug reactions in a cohort of patients treated with PD-1/PD-L1 inhibitors in real-world practice

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Background: Data related to adverse drug reactions (ADRs), specifically immune-related adverse events (irAEs), in long-term treatment with immunotherapy in real-world practice is scarce, as is general information regarding the management of ADRs.

Objectives: To characterize and describe the incidence of ADRs in patients who began immunotherapy treatment in clinical practice.

Methods: In a prospective observational study cancer patients ≥18 years of age who were treated with a monotherapy regime of PD-1/PD-L1 inhibitors were evaluated. The study period was from November 2017 to June 2019 and patients were followed up until June 2021. Patients were contacted monthly by telephone and their electronic health records were reviewed. Each ADR was graded according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0).

Results: Out of 99 patients, 86 met the inclusion criteria. Most were male (67.4%), with a median age of 66 (interquartile range, IQR: 59–76). The most frequent cancer was non-small cellular lung cancer (46 cases, 53.5%), followed by melanoma (22, 25.6%). A total of 74 patients (86%) were treated with anti-PD-1 drugs and 12 (14%) were treated with anti-PD-L1 drugs. The median treatment durations were 4.9 (IQR: 1.9–17.0) and 5.9 months (IQR: 1.2–12.3), respectively. Sixty-three patients (73%) developed from a total of 156 (44% of the total number of ADR) irADRs, wherein the most frequent were skin disorders (50 cases, 32%, incidence = 30.5 irADRs/100 patients per year [p-y]), gastrointestinal disorders (29, 19%, 17.7 irADRs/100 p-y), musculoskeletal

disorders (17, 11%, 10.4 irADRs/100 p-y), and endocrine disorders (14, 9%, 8.6 irADRs/100 p-y). A total of 22 irADRs (14%) had a latency period of ≥12 months. Twelve irADRs (7.7%) were categorized as grade 3–4, and while 2 (1.3%) were categorized as grade 5 (death). Sixty-one irADRs (39.1%) in 36 patients required pharmacological treatment and 47 irADRs (30.1%) in 22 patients required treatment with corticosteriods.

Conclusion: The majority of patients treated with anti-PD1/PDL1-based immunotherapy experienced adverse reactions. Although most of these reactions were mild, 11.5% were categorized as grade 3 or above. A high percentage of the reactions were immune-related and occurred throughout the treatment, thereby indicating that early identification and close monitoring is essential.

KEYWORDS

immunotherapy, adverse reaction, immune-related adverse reaction, pharmacovigilance, real-world practice

Introduction

Since their initial approval by the European Medicines Agency (EMA), the use of immunotherapy drugs in different cancer indications has increased gradually. As such, there is a requirement to detect the occurrence of adverse drug reactions (ADRs), and in particular, immune-related adverse events (irAEs), when these treatments are used over a prolonged period of time in real-world clinical practice.

Immune checkpoint inhibitors (CPIs), such as the cytotoxic T lymphocyte associated antigen-4 (CTLA-4) antibody ipilimumab and the programmed cell death (PD-1)/programmed cell death ligand-1 (PD-L1) antibodies nivolumab, pembrolizumab, and atezolizumab, were the first drugs approved for use in immunotherapy to treat cancer (1–3). More specifically, in May 2017, nivolumab and pembrolizumab were approved for some indications, such as advanced melanoma, non-small cell lung cancer, Hodgkin's lymphoma, and bladder urothelial cancer. Later, these antibodies were also approved for renal cell carcinoma and squamous head and neck cancers. In addition, atezolizumab, which was initially approved for non-small cell lung cancer and bladder urothelial cancer, was also later approved for additional indications, namely small cell lung cancer, triple-negative breast cancer, and hepatocellular carcinoma. The treatment of other types of cancer by anti-PD-1/PD-L1 drugs alone, or in combination with immunotherapeutic and non-immunotherapeutic drugs, has also been approved more recently (4).

Due to the fact that immunotherapy treatment stimulates the natural immune defence against cancer cells, its adverse effects are related to immune responses of normal cells. Although anti-PD-1 drugs are overall less toxic than other oncologic treatments, such as standard chemotherapy, irAEs have been described in several clinical trials. For example, adverse effects related to organ-specific immune mechanisms have been described, including colitis, hepatitis, pneumonitis, and hypothyroidism, as well as general adverse events related to immune activation, including fatigue, diarrhoea, and dermatitis. Other less frequent adverse effects potentially attributable to immune mechanisms, such as musculoskeletal problems or neurologic alterations, have also been described in patients treated with immunotherapy. Although the real frequency of these rare adverse effects is not known, they may negatively impact a patient's quality of life, and so a better understanding of irAEs is necessary to determine the risk–benefit ratio for each patient when prescribing anti-PD-1/PD-L1 drugs (5).

Moreover, since treatment with anti-PD-1 or anti-PD-L1 therapies can require months or years to complete, it is also important to know the frequency of such adverse effects over the duration of treatment. Although these effects could appear at any time during treatment, it has been reported that those related to skin, gastrointestinal, and hepatic reactions tend to appear earlier than those related to the pulmonary, endocrine, and renal systems (6). Given that such information is scarce, physicians should be aware of how to manage patients who suffer from irAEs during treatment. Indeed, despite the relatively low rates of high-grade side effects with these treatments (usually ∼10%), some can be life-threatening and require urgent and appropriate management (7). In addition, since immunotherapy treatment is being gradually expanded to patients with earlier-stage cancer and thus, longer life expectancies, the collection of such information becomes paramount (8).

Currently, the available information related to the management of immune toxicity is obtained from the meta-analysis of randomised clinical trials and from observational retrospective studies or case reports, but prospective information on the detection and management of the toxicity is lacking (4, 9, 10).

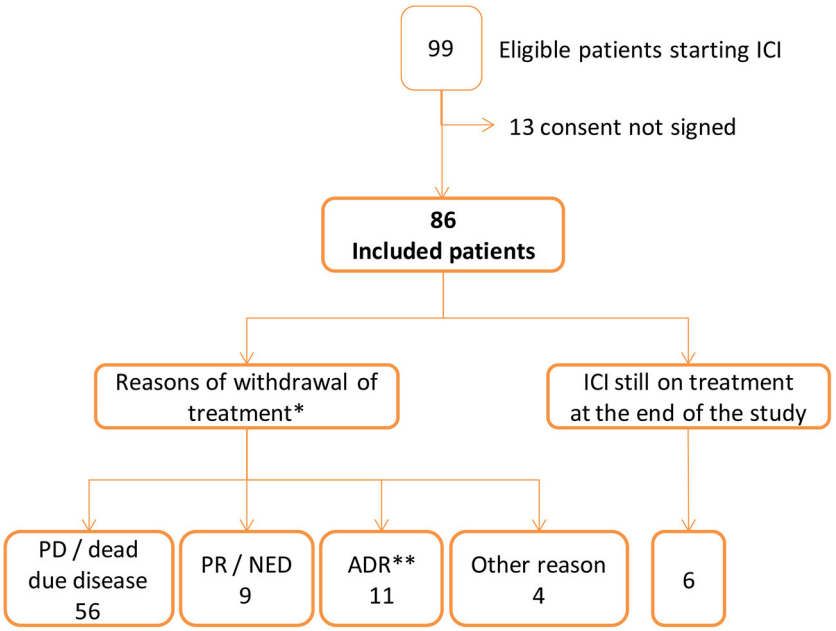

FIGURE 1
Flow chart of patients starting immune checkpoint inhibitors (ICI). *PD, progression disease; PR, partial response; NED, no-evidence disease; ADR, adverse drug reaction. **ADR was the only reason for ending treatment in 6 patients: adrenal insufficiency and cholestatic liver injury (1), acute renal insufficiency (1), interstitial pneumonitis (1), bipulmonary infiltrates (1), hypopituitarism (1), autoimmune colitis and cytomegalovirus gastrointestinal infection (1). In 5 patients there were additional reasons: pruritus and PD (1), adrenal insufficiency and PD (1), hyperamylasaemia and NED (1), dermatitis psoriasiform and rash and PR (1) and diarrhoea and PR (1). Other reasons of ending ICI treatment were appendicitis (1 patient), ictus (1), patient withdraw consent at the third visit (1), cognitive impairment identified at the second visit (1).

The aim of our study is therefore to characterise and describe the incidence of adverse reactions occurring in patients who began immunotherapy treatment in clinical practice at our institution, specifically focusing on those who underwent treatment with an anti-PD1/PDL1 monotherapy and focusing on the frequency of irADRs.

Materials and methods

This prospective observational study evaluated cancer patients who were consecutively treated in real-world practice with monotherapy of PD-1/PD-L1 checkpoint inhibitors (standard schedules) from November 2017 to June 2019, wherein patient follow-up was continued until June 2021, regardless of the treatment line employed. The patients were followed until treatment interruption or until the end of the study. The study was conducted at the Vall d'Hebron University Hospital (Catalunya, Spain) and the study protocol was approved by the Ethical Committee of the same hospital (16/6/2017).

The inclusion criteria included patients ≥18 years of age who began treatment with nivolumab or pembrolizumab following a diagnosis of metastatic non-small cell lung cancer, advanced melanoma, or advanced renal cancer. Eight months after the study was commenced, an amendment was made to the protocol, and patients treated with atezolizumab were included. Other indications were also added to the protocol at this point, including squamous cell head and neck cancers, and urothelial carcinoma (advanced or metastatic). Patients treated with other immunotherapy drugs or with a combination of such drugs were excluded, as were those participating in clinical trials.

Data sources

Patients were identified using the daily treatment list of the pharmacy service and were included after signing and documenting their informed consent. Each patient was contacted monthly by telephone and was interviewed in relation to the occurrence of adverse reactions. A structured questionnaire was employed for this purpose. The monthly telephone interview carried out to obtain information related to any adverse effects began with an open question, followed by some symptom-focused questions (e.g., related to organ-specific irADRs, including colitis, hepatitis, pneumonitis, and hypothyroidism, as well as more general adverse reactions related to immune activation, including fatigue, diarrhoea, and dermatitis). To obtain further information, the patient's electronic health record and laboratory test results (i.e., the

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TABLE 1 General characteristics of patients.

Included patients, *n* (%)	NSCLC 46 (53.5)	Melanoma 22 (25.6)	Head and neck 9 (10.5)	Renovesical 9 (10.5)	Total 86 (100)
Age, median (IQR) (min-max), years	66.5 (60–72) (41–87)	74 (63–80) (39–88)	57 (54–62) (50–65)	72 (58–78) (38–85)	66 (59–76) (38–88)
Gender, male/female, *n* (%)	30 (65.2)/16 (34.8)	12 (54.5)/10 (45.5)	8 (88.9)/1 (11.1)	8 (88.9)/1 (11.1)	58 (67.4)/28 (32.6)
Charlson CIS, median (IQR) (min-max)	5 (3–8) (2–14)	4 (2–6) (2–11)	3 (2–4) (2–5)	6 (3–8) (2–14)	4 (2–6) (2–14)
Treatment, 1stL / 2$^{\circ n}$L or more, n (%)	7 (15.2)/39 (84.8)	17 (77.3)/5 (22.7)	3 (33.3)/6 (66.7)	0/9 (100)	27 (31.4)/59 (68.6)
Anti-PD-1	7 (15.2)/28 (60.9)	17 (77.3)/5 (22.7)	3 (33.3)/6 (66.7)	0/8 (88.9)	27 (31.4)/47 (54.7)
Anti-PD-L1	0/11(23.91)	0/0	0/0	0/1(11.11)	0/12 (14.0)
Duration of treatment, median (IQR) (min-max), months	2.7 (1.4–12.2) (0.0–33.4)	9.7 (3.5–11.5) (1.0–30.1)	15.2 (2.7–28.0) (0.5–39.3)	3.9 (2.8–24.2) (0.0–41.0)	4.9 (1.5–16.4) (0.0–41.0)
Anti-PD-1	2.4 (1.4–12.6) (0.0–33.4)	9.7 (3.5–11.5) (1.0–30.1)	15.2 (2.7–28.0) (0.5–39.3)	3.6 (2.6–22.1) (0.0–41.0)	4.9 (1.9–17.0) (0–41)
Anti-PD-L1	4.2 (1.0–8.2) (0.7–18.9)	-	-	31.3 (31.3–31.3) (31.3–31.3)	5.9 (1.2–12.3) (0.7–31.3)
Reasons to stop the treatment, *n* (%)*	45 (97.8)	21 (95.5)	7 (77.8)	7 (77.8)	80 (93.0)
PD/death	36 (80.0)	8 (38.1)	6 (85.7)	6 (85.7)	56 (70.0)
ADR	6 (13.3)	4 (19.1)	1 (14.3)	0	11 (13.8)
NED/PR	3 (6.7)	6 (28.6)	0	0	9 (11.3)
Other reasons**	0	3 (14.3)	0	1 (14.3)	4 (5.0)
Still on treatment at the end of the study, *n* (%)	1 (2.2)	1 (4.6)	2 (22.2)	2 (22.2)	6 (7.0)

Charlson Comorbidity Index Score (0–36).
*PD, Progression disease or death related to cancer; NED, no evidence of disease; PR, partial response; ADR, adverse drug reaction. ADR was the only cause of withdrawal in 6 patients.
**Other reasons: appendicitis (1), ictus (1), patient withdraw consent (1), cognitive impairment identified at the second visit (1).
NSCLC, Non-small cell lung cancer.

results of blood tests, diagnostic imaging, or pathological anatomy assessments) were periodically reviewed. All patients were followed until 1 month after the end of treatment, irrespective of the reason for discontinuing treatment (e.g., disease progression, adverse effects, death, or other). However, some adverse effects were followed up until the end of the study to obtain further information regarding the treatment outcome. A total of 86 patients were included, thereby allowing us to estimate the ADR occurrence proportion with a precision of ±10%.

Outcome measures

Information regarding the demographic and clinical variables was collected from the clinical medical records, as were variables related to the cancer (i.e., cancer type, date of diagnosis, stage of cancer upon commencing immunotherapy treatment, and number of previous treatment lines). Complete information related to the immunotherapy treatment employed and regarding other concomitant treatments was also gathered (i.e., type of drug, dosage, and the start/end treatment dates).

The primary outcome of our study was the characterisation of the ADRs experienced by cancer patients following the initiation of immune checkpoint therapy. The definition of ADRs used for the purpose of this study was as that stated in the European and Spanish regulations (11, 12). Literature data corresponding to immune-related adverse drug reactions (irADRs) were used to classify the ADRs as irADRs (8, 13, 14).

For each adverse effect, the onset date, severity, whether any additional treatment was required, and the outcome were registered. We used the Common Terminology of Clinical Adverse Events version 5.0 (CTCAE v5.0) of the Cancer National Institute categorisation to identify grades 3–5 as serious and grades 1–2 for all other reactions (15). In addition, the severity of each adverse effect was classified according to the European Union criteria (16). The MedDRA dictionary of medical terminology was used to classify the ADRs, while the drugs used for treatment were classified according to the Anatomical Chemical Classification (ATC) system (17, 18).

The imputability analysis of the drugs and the evaluation of any causal relationship between the drugs and the suspected adverse reactions were analysed using the methods and algorithm provided by the Spanish Pharmacovigilance System (SEFV) (19).

Data analysis

The frequencies and incidences of all ADRs and irADRs were calculated during the study period. In addition, the ADR frequency was analysed by taking into account the

TABLE 2 Adverse drug reactions by system organ class disorders.

System organ class	irADRs *n* (%)	Patients* *n* (%)	non irADRs *n* (%)	Patients* *n* (%)	All ADRs *n* (%)	Patients* *n* (%)
Skin and subcutaneous tissue	50 (32.1)	34 (54.0)	2 (1.0)	2 (3.0)	52 (14.7)	36 (48.0)
Alopecia	1	1	0	0	1	1
Dermatitis psoriasiform	1	1	0	0	1	1
Dry skin	10	10	0	0	10	10
Eczema	1	1	0	0	1	1
Erythema	4	4	0	0	4	4
Exfoliative rash	1	1	0	0	1	1
Hyperhidrosis	0	0	1	1	1	1
Hyperkeratosis	1	1	0	0	1	1
Nail discolouration	1	1	0	0	1	1
Nail growth abnormal	1	1	0	0	1	1
Penile ulceration	1	1	0	0	1	1
Plantar erythema	1	1	0	0	1	1
Pruritus	16	16	0	0	16	16
Rash	5	5	0	0	5	5
Rash pruritic	2	2	0	0	2	2
Seborrhoeic dermatitis	1	1	0	1	1	2
Skin exfoliation	2	2	0	0	2	2
Vitiligo	1	1	0	0	1	1
General and administration site cond.	3 (1.9)	3 (4.8)	46 (23.4)	35 (53.0)	49 (13.9)	36 (48.0)
Asthenia	0	0	13	13	13	13
Fatigue	0	0	16	16	16	16
Feeling cold	0	0	3	3	3	3
Gait disturbance	0	0	1	1	1	1
Malaise	0	0	1	1	1	1
Mucosal dryness	3	3	0	0	3	3
Oedema peripheral	0	0	4	4	4	4
Pyrexia	0	0	7	7	7	7
Thirst	0	0	1	1	1	1
Gastrointestinal	29 (18.6)	21 (33.3)	18 (9.1)	15 (22.7)	47 (13.3)	33 (44.0)
Abdominal pain	0	0	2	2	2	2
Autoimmune colitis	1	1	0	0	1	1
Constipation	0	0	6	6	6	6
Dental dysaesthesia	0	0	1	1	1	1
Diarrhoea	13	12	0	0	13	12
Dry mouth	10	10	0	0	10	10
Lip oedema	0	0	2	1	2	1
Nausea	0	0	6	6	6	6
Stomatitis	5	5	0	0	5	5
Vomiting	0	0	1	1	1	1
Infections and infestations	1 (0.6)	1 (1.06)	39 (19.8)	25 (37.9)	40 (11.3)	25 (33.3)
Bronchitis	0	0	4	3	4	3
Campylobacter gastroenteritis	0	0	1	1	1	1
Conjunctivitis	0	0	2	2	2	2
Conjunctivitis viral	0	0	1	1	1	1
Cytomegalovirus gastrointestinal infection	0	0	1	1	1	1

(Continued)

TABLE 2 Continued

System organ class	irADRs *n* (%)	Patients* *n* (%)	non irADRs *n* (%)	Patients* *n* (%)	All ADRs *n* (%)	Patients* *n* (%)
Herpes zoster	0	0	1	1	1	1
Hordeolum	0	0	2	1	2	1
Influenza	0	0	1	1	1	1
Lower respiratory tract infection	0	0	1	1	1	1
Lower respiratory tract infection bacterial	0	0	1	1	1	1
Onychomycosis	0	0	1	1	1	1
Oral herpes	0	0	1	1	1	1
Oral infection	0	0	1	1	1	1
Other	0	0	1	1	1	1
Otitis externa	0	0	1	1	1	1
Peritonsillar abscess	0	0	1	1	1	1
Pneumonia	0	0	2	2	2	2
Respiratory tract infection	0	0	5	5	5	5
Rhinitis	1	1	0	0	1	1
Staphylococcal skin infection	0	0	1	1	1	1
Tooth abscess	0	0	1	1	1	1
Upper respiratory tract infection	0	0	4	3	4	3
Urinary tract infection	0	0	4	4	4	4
Urosepsis	0	0	1	1	1	1
Metabolism and nutrition	3 (1.9)	3 (4.8)	25 (12.7)	24 (36.4)	28 (7.9)	25 (33.3)
Abnormal loss of weight	0	0	2	2	2	2
Decreased appetite	0	0	14	14	14	14
Diabetic ketoacidosis	1	1	0	0	1	1
Hyperamylasaemia	2	2	0	0	2	2
Hypercholesterolaemia	0	0	3	3	3	3
Hyperkalaemia	0	0	2	2	2	2
Hypomagnesaemia	0	0	1	1	1	1
Hyponatraemia	0	0	1	1	1	1
Polydipsia	0	0	2	2	2	2
Musculoskeletal and connective tissue	17 (10.9)	16 (25.4)	5 (2.5)	5 (7.6)	22 (6.2)	18 (24.0)
Arthralgia	8	7	0	0	8	7
Bursitis	0	0	1	1	1	1
Muscle rigidity	0	0	1	1	1	1
Muscle spasms	0	0	2	2	2	2
Musculoskeletal pain	3	3	0	0	3	3
Myalgia	4	4	0	0	4	4
Osteonecrosis	0	0	1	1	1	1
Polyarthritis	1	1	0	0	1	1
Tendon pain	1	1	0	0	1	1
Respiratory, thoracic and mediastinal	10 (6.4)	8 (12.7)	12 (6.1)	11 (16.7)	22 (6.2)	17 (22.7)
Acute interstitial pneumonitis	1	1	0	0	1	1
Cough	0	0	5	5	5	5
Increased viscosity of upper respiratory secretion	0	0	1	1	1	1
Lung infiltration	1	1	0	0	1	1
Organising pneumonia	1	1	0	0	1	1
Pneumonitis	1	1	0	0	1	1

(Continued)

TABLE 2 Continued

System organ class	irADRs *n* (%)	Patients* *n* (%)	non irADRs *n* (%)	Patients* *n* (%)	All ADRs *n* (%)	Patients* *n* (%)
Productive cough	0	0	3	3	3	3
Pulmonary embolism	0	0	1	1	1	1
Respiratory failure	0	0	1	1	1	1
Rhinorrhoea	4	4	0	0	4	4
Suffocation feeling	0	0	1	1	1	1
Throat irritation	2	2	0	0	2	2
Nervous system	0	0	19 (9.6)	17 (25.8)	19 (5.4)	17 (22.7)
Balance disorder	0	0	1	1	1	1
Dizziness	0	0	1	1	1	1
Dysgeusia	0	0	3	3	3	3
Headache	0	0	3	3	3	3
Paraesthesia	0	0	9	9	9	9
Tonic clonic movements	0	0	1	1	1	1
Tremor	0	0	1	1	1	1
Endocrine	14 (9.0)	13 (20.6)	0	0	14 (4.0)	13 (17.3)
Adrenal insufficiency	6	6	0	0	6	6
Hypophysitis	1	1	0	0	1	1
Hypopituitarism	1	1	0	0	1	1
Hypothyroidism	6	6	0	0	6	6
Eye	12 (7.7)	8 (12.7)	2 (1.0)	2 (3.0)	14 (4.0)	10 (13.3)
Conjuctival hyperaemia	1	1	0	0	1	1
Corneal disorder	1	1	0	0	1	1
Corneal erosion	1	1	0	0	1	1
Dry eye	3	3	0	0	3	3
Eye pruritus	2	2	0	0	2	2
Eyelid cyst	1	1	0	0	1	1
Photophobia	1	1	0	0	1	1
Presbyopia	0	0	1	1	1	1
Vision blurred	2	2	0	0	2	2
Vitreous floaters	0	0	1	1	1	1
Blood and lymphatic system	3 (1.9)	3 (4.8)	11 (5.6)	7 (10.6)	14 (4.0)	10 (13.3)
Anaemia	0	0	6	6	6	6
Eosinophilia	2	2	0	0	2	2
Leukocytosis	0	0	1	1	1	1
Lymphopenia	0	0	2	2	2	2
Neutrophilia	0	0	1	1	1	1
Thrombocytopenia	1	1	0	0	1	1
Thrombocytosis	0	0	1	1	1	1
Hepatobiliary	12 (7.7)	10 (15.9)	0	0	12 (3.4)	10 (13.3)
Cholestasis	3	3	0	0	3	3
Cholestatic liver injury	6	6	0	0	6	6
Hepatocellular injury	3	2	0	0	3	2
Renal and urinary	2 (1.3)	2 (3.2)	6 (3.0)	6 (9.1)	8 (2.3)	8 (10.7)
Other	0	0	3	3	3	3
Renal failure	0	0	2	2	2	2
Renal impairment	1	1	0	0	1	1

(Continued)

TABLE 2 Continued

System organ class	irADRs *n* (%)	Patients* *n* (%)	non irADRs *n* (%)	Patients* *n* (%)	All ADRs *n* (%)	Patients* *n* (%)
Tubulointerstitial nephritis	1	1	0	0	1	1
Urinary incontinence	0	0	1	1	1	1
Psychiatric	0	0	6 (3.0)	6 (9.1)	6 (1.7)	6 (8.0)
Apathy	0	0	2	2	2	2
Depression	0	0	1	1	1	1
Depressive symptom	0	0	1	1	1	1
Other	0	0	1	1	1	1
Terminal insomnia	0	0	1	1	1	1
Vascular	0	0	5 (2.5)	5 (7.6)	5 (1.4)	5 (6.7)
Hypertension	0	0	3	3	3	3
Hypotension	0	0	1	1	1	1
Thrombophlebitis	0	0	1	1	1	1
Neoplasms benign, malignant and NOS[a]	0	0	1 (0.5)	1 (1.5)	1 (0.3)	1 (1.3)
Basal cell carcinoma	0	0	1	1	1	1
Total	156 (100)	63 (100)	197 (100)	66 (100)	353 (100)	75 (100)

*Patients may have more than one ADR.
[a]NOS, not otherwise specified; ADR, adverse drug reactions; irADR, immunorelated adverse drug reaction.

following criteria: the affected organ/system, the reaction seriousness, whether the reaction was immune-related or late-onset immune-related, and the drug treatment employed.

The ADR outcomes were described along with the type of treatment and the reason for discontinuing treatment. For analysis of the ADR management protocol, four categories were considered: non-intervention or hygienic-dietetic measures, surgery, transfusion, and pharmacological measures.

The reaction frequencies and proportions were used for the descriptive analysis of the categorical variables, while the median, the Q1 and Q3 quartile values, and the minimum/maximum values were used for the continuous variables.

The ADR incidences were calculated by dividing the number of ADRs by the corresponding time in treatment and were expressed in cases per 100 patients per year (p-y) of exposure; the 95% confidence intervals were estimated from the Poisson distribution.

The analyses were performed using SAS® 9.4 software (SAS Institute Inc., Cary, NC, United States).

Results

General patient characteristics

Out of the 99 patients identified, 86 met the inclusion criteria. The total cohort follow up was a median of 5.68 months (IQR: 2.8–20). The majority were male (67.4%), with a median age of 66 years (IQR: 59–76), and the median Charlson comorbidity index was 4 (IQR: 2–6). The most frequent cancer was non-small cellular lung cancer (46 cases, 53.5%), followed by melanoma (22 cases, 25.6%). Twenty-seven patients (31.4%) received a first line treatment (Figure 1, Table 1). Fourteen patients (16%) suffered from a locally advanced disease, and 72 (84%) exhibited metastasis.

A total of 74 patients (86%) were treated with anti-PD-1 drugs and 12 (14%) were treated with anti-PD-L1 drugs. The median treatment durations were 4.9 (IQR: 1.9–17.0) and 5.9 months (IQR: 1.2–12.3), respectively (Table 1).

Treatment was stopped in 80 patients for the following reasons: i) 56 patients (70%), disease progression or death; ii) 11 patients (14%), the occurrence of an ADR; iii) 9 patients (11%), no evidence of disease (complete response) or a partial response; and iv) 4 patients (5%), other reasons. A total of 6 patients were still under treatment at the end of the study (median 31 months, IQR 27.9–33.4) (Figure 1, Table 1).

Adverse drug reactions: Overall and immune-related reactions

During the follow-up, 75 patients (87.2%) were found to have reported a total of 353 ADRs, representing a global incidence of 215.5 ADRs/100 p-y following treatment (CI 95%: 194.2–239.2). Skin reactions (52 cases, 15%), general disorders (49 cases, 14%) (such as asthenia, fatigue andpyrexia), and gastrointestinal disorders (47 cases, 13%) were the most frequent (Table 2).

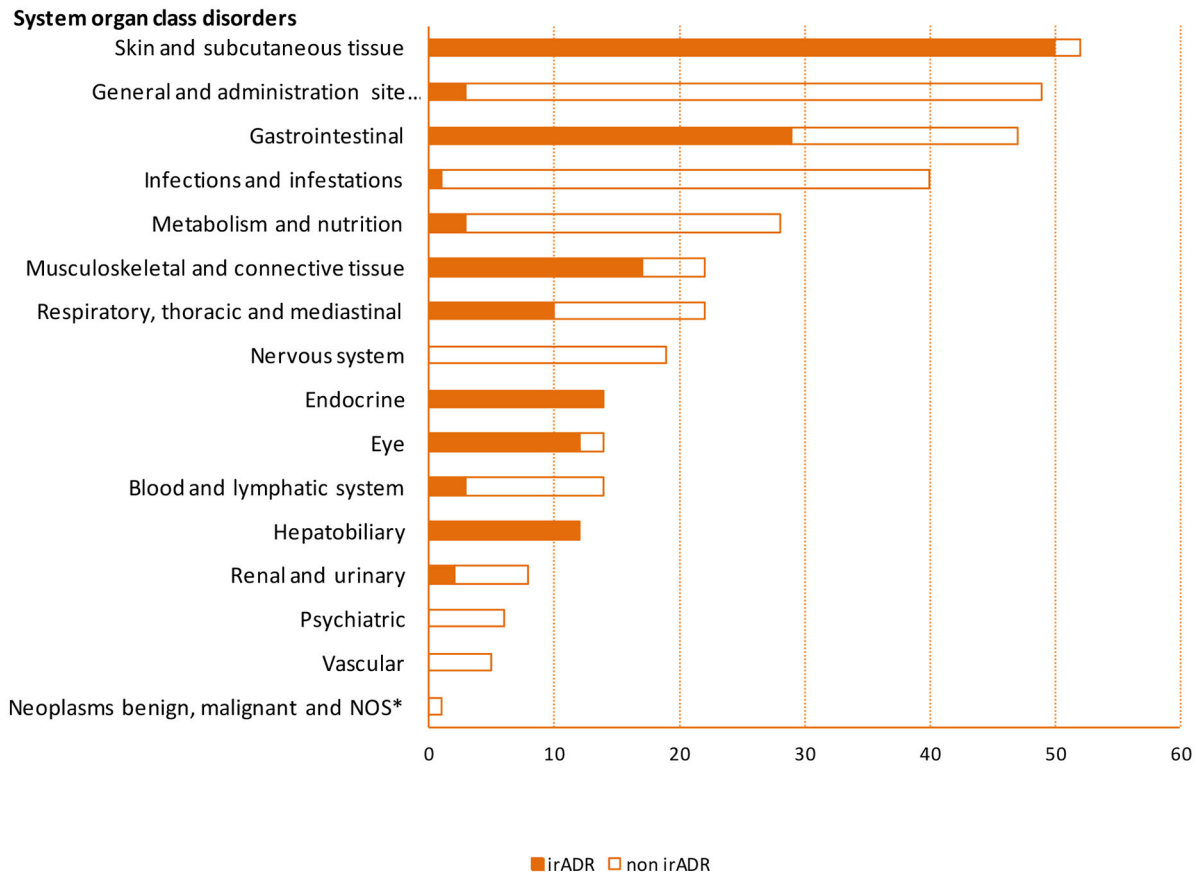

FIGURE 2
Frequency of adverse drug reactions by system organ class disorders. *NOS, not otherwise specified; irADR, immune-related adverse drug reaction.

In 63 patients (73%), a total of 156 (44% of the total number of ADR) irADRs were recorded, representing an incidence of 95.3 irADRs/100 p-y (CI 95%: 81.4–111.4). More specifically, skin disorders (50 cases, 32% of the 156 irADRs) with an incidence of 30.5 irADRs/100 p-y (23.1–40.3), gastrointestinal disorders (29 cases, 19%) with an incidence of 17.7 irADRs/100 p-y (12.3–25.5), musculoskeletal disorders (17 cases, 11%) with an incidence of 10.4 irADRs/100 p-y (6.5–16.70), and endocrine disorders (14 cases, 9%) with an incidence of 8.6 irADRs/100 p-y (5.1–14.4) were the most frequent (Figure 2, Supplementary Table S1).

Of the overall ADRs, in 45 cases (12% of the total number of ADRs) the latency period was ≥12 months, while a total of 22 irADRs (14% of the total number of irADRs) had a latency period of ≥12 months. Of these, 8 irADRs (27.6% of total gastrointestinal irADRs) affected the gastrointestinal system, 4 affected the eyes (33.3% of total eye irADRs), 4 affected skin and subcutaneous tissue (8% of total skin and subcutaneous irADRs) and 2 affected the renal and urinary system (100% of the renal and urinary system irADRs) (Figure 3, Supplementary Table S2). The detailed reactions, and all their characteristics are described in Table 3.

Regarding the seriousness of the reactions, 37 ADRs (10.5%) were categorized as grades 3–4, and 3 (1%) were categorized as grade 5 (death). Twelve of the irADRs (7.7%) were categorized as grades 3–4, and of these, 4 were diarrhoea, 3 were hepatocellular injuries, and the remainder consisted of one each of the following: diabetic ketoacidosis, hyperamylasaemia, polyarthritis, acute interstitial and tubulointerstitial nephritis, and pneumonitis. Only 2 irADRs (1.3%) were categorized as grade 5 (autoimmune colitis and hypopituitarism), the autoimmune colitis had a late presentation (>12 months) (Tables 3, 4, Supplementary Table S1).

In terms of ADR management, pharmacological treatment was required for 147 ADRs (41.7%) in 58 patients (77.3%), while 199 ADRs (56.5%) in 68 patients required no intervention

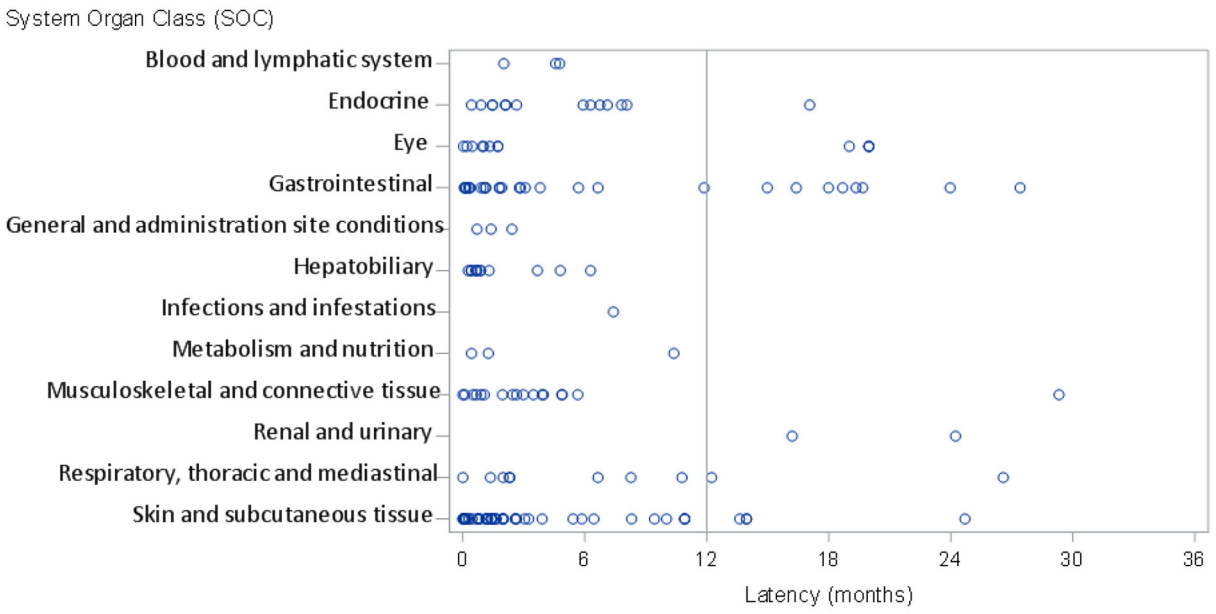

FIGURE 3
Latency period of immune-related adverse reactions.

or only hygienic-dietetic measures. In addition, 61 irADRs (39.1%) in 36 patients required pharmacological treatmen and, of these, 47 irADRs (30.1%) in 21 patients required treatment with corticosteroids, including oral and topical treatments. In only one case did the irADR require treatment with infliximab (Table 5, Supplementary Table S3). Additionally, in 13 patients treated with corticosteroids, it was necessary to interrupt the immunotherapy treatment; this interruption was permanent for 7 patients and temporary for the remainder.

In terms of the ADR outcome, in 272 of the total ADRs (77.1%), a "recovered" outcome was recorded, as was also the case for 111 (71.2%) of the irADRs. There were a total of 46 ADRs (13%) and 23 irADRs (14.7%) with a "non-recovered" outcome (Table 4).

Discussion

In the present study we characterised the occurrence of ADRs, specifically irADRs, in cancer patients treated with immunotherapy in real-world clinical practice. The majority of patients experienced adverse reactions (87.2%), although most reactions were mild, with only 11.5% being categorized as grade 3 or above. A high percentage of the ADRs (44%) were immune-related, with skin disorders, gastrointestinal disorders, musculoskeletal disorders, and endocrine reactions being the most frequent. It is important to describe these results as they may have major implications for clinicians across multiple specialities who manage the rare, but clinically important, organ-specific irADRs.

In our study, the percentage of patients suffering from irADRs was found to be similar to that described by Nigro et al. in their retrospective study (76%), but higher than that reported by Majzoub et al. who quoted a figure of only 25% (9, 10). The criteria used for categorisation of the ADRs as immune-related based on the organ/system involved or through the literature identification, could explain these differences. In addition, intensive monitoring methods (monthly contact by telephone and structured interviews) were used in our study to identify patients suffering from irADRs, and such frequent contact could also account for the identification of greater numbers of affected patients. Regarding the severity of the irADRs, a similar percentage of irADRs was categorized as grade 3 or above in our study compared to that reported by Nigro et al. (i.e., 9.6%) (9). However, based on a meta-analysis involving 125 clinical trials, Y. Wang et al. reported that 14% of irADRs were grade 3 or above (20). These differences could be explained by considering the means by which the adverse reactions were selected, since in the above meta-analysis, all adverse events were gathered, whereas in our study, only the adverse drug reactions were evaluated.

Of the various irADRs described in the present study, the most frequent reactions were those affecting the skin, followed by general disorders, and those affecting the gastrointestinal system. These results are consistent with those described in the two retrospective studies and in both meta-analyses by Y. Wang et al. and P.F. Wang et al., wherein diarrhoea, colitis, and skin

TABLE 3 Characteristics of late immune-related ADRs.

	Severity	Management
Endocrine		
Hypothyroidism	G1	Chronic treatment with Levothyroxine. Immunotherapy was continued.
Eye		
Conjunctival hyperaemia	G2	No treatment required. Immunotherapy withdrawn for another reason. Recovered
Corneal disorder	G1	Eye lubricating drops. Immunotherapy was continued. Recovered
Corneal erosion	G1	Ocular antibiotic treatment. Immunotherapy was continued. Recovered
Eyelid cyst	G2	Surgery. Immunotherapy was continued. Recovered
Gastrointestinal		
Autoimmune colitis	G5	Prednisone and infliximab treatment. Immunotherapy withdrawal. Death
Diarrhoea	G3	Serum therapy and antidiarrheal treatment. Immunotherapy was delayed for a week. Recovered
Diarrhoea	G3	Antidiarrheal treatment. Immunotherapy was continued. Recovered
Diarrhoea	G3	Serum and antidiarrheal treatment. Immunotherapy withdrawal for PD. Recovered
Diarrhoea	G2	Hygienic-dietetic measures. Immunotherapy was continued. Recovered
Diarrhoea	G2	Treatment with prednisone. Immunotherapy completed. Not recovered.
Diarrhoea	G1	Antidiarrheal treatment. Immunotherapy delayed for a week. Recovered
Stomatitis	G2	Nystatin treatment. Immunotherapy was continued. Recovered
Musculoskeletal and connective tissue		
Arthralgia	G1	No treatment required. Immunotherapy stopped for another reason. Recovered.
Renal and urinary		
Renal impairment	G1	Serum therapy. Immunotherapy continued. Recovered
Tubulointerstitial nephritis	G3	Prednisone treatment. Immunotherapy withdrawal for PD. Recovered
Respiratory, thoracic and mediastinal		
Lung infiltration	G2	No treatment required. Immunotherapy withdrawal. Recovered.
Pneumonitis	G1	No treatment required. Immunotherapy delayed for a week. Recovered.
Skin and subcutaneous tissue		
Dermatitis psoriasiform	G2	Prednisone and topical antiinfective treatment. Immunotherapy withdrawal for symptoms persistence. Recovered
Dry skin	G1	Hygienic-dietetic measures. Immunotherapy continued. Recovered
Pruritus	G1	Hygienic-dietetic measures. Immunotherapy continued. Recovered
Pruritus	G1	No treatment required. Immunotherapy withdrawal for another adverse drug reaction (worsening of renal impairment). Recovered

disorders were among the most frequently reported reactions (9, 10, 19, 21).

Importantly, it should be mentioned that although endocrinopathies associated with immunotherapy are not the most common irADRs reported in clinical trials, if they fail to be quickly and accurately recognised, they have the potential to become life-threatening. In this context, we note that a relatively high percentage and incidence of endocrine-related irADRs (i.e., 9%) were reported in our study, while in the meta-analysis by P.F. Wang et al., endocrine irADRs were reported for <2% of treated patients (20). Surprisingly, our data show that adrenal insufficiency and, hypothyroidism, were the most frequent endocrine-related irADR, with an incidence of 3.66 ADRs/100 p-y each. The occurrence of adrenal insufficiency was lower in the published meta-analysis by Y. Wang et al. (0.7%), and was not described in that published by Baxi et al. (4, 19). In our study, the information related to the diagnosis of adrenal insufficiency was collected from the medical records of patients; however, we cannot rule out the possibility that some of these cases were secondary to hypophysitis. Based on the above analyses, it is therefore apparent that intensive surveillance is necessary to diagnose these irADRs, and this is of particular importance since these cases may present with non-specific symptoms (8).

In terms of pneumonitis, we found a frequency of 3% when all presentations were included (i.e., interstitial pneumonitis, lung infiltration, and organised pneumonia). This proportion is similar to those reported in previous studies, such as in the meta-analysis by Y. Wang et al. (i.e., 2.8%) (19). However, we note that in a retrospective study by Majzoub et al., the percentage

TABLE 4 Adverse drug reactions, severity, and outcome.

Adverse drug reactions n (%)	All ADRs 353 (100)	All irADRs 156 (44.47)	Early-irADRs 134 (100)	Late-irADRs 22 (100)
ICI treatment				
Anti-PD-1	301 (85.3)	134 (85.9)	114 (85.1)	20 (90.9)
Anti-PD-L1	52 (14.7)	22 (14.1)	20 (14.9)	2 (9.1)
Severity of ADRs				
G1–G2	313 (88.7)	142 (91.0)	125 (93.3)	17 (77.3)
G3–G4	37 (10.5)	12 (7.7)	8 (5.9)	4 (18.2)
G5	3 (0.9)	2 (1.3)	1 (0.8)	1 (4.5)
Outcome				
Recovered	272 (77.1)	111 (71.2)	92 (82.9)	19 (17.1)
Recovering	27 (7.7)	19 (12.2)	17 (89.5)	2 (10.5)
Not recovered	46 (13.0)	23 (14.7)	23 (100)	0
Death	3 (0.9)	2 (1.3)	1 (50.0)	1 (50.0)
Unknown	5 (1.4)	1 (0.6)	1 (100)	0

ADRs, Adverse drug reactions; irADRs, immune-related ADRs; early-irADRs, immune-related ADRs with a latency period less than 12 months; late-irADRs, immune-related ADRs with a latency period equal or greater than 12 months.

varied from 7.1% with nivolumab to 3.2% with ipilimumab (10). Despite its relatively low instance, pneumonitis is potentially life-threatening, and so surveillance is also necessary for this particular irADR. It should be noted here that for the purpose of our study, we did not include patients who had received combinations with ipilimumab.

Regarding the latency period, which is considered to be one of the areas of uncertainty, our data suggested that 14% of the irADRs appeared after 12 months from the start of treatment. However, Nigro et al. found that 30% of patients presented with a late-onset irADR. These differences may be due to the inclusion criteria employed in each study, since in the study by Nigro et al., only patients with a minimum treatment duration of 12 months were included. In contrast, in a high proportion of patients included in our study (65%), it was necessary to interrupt immunotherapy due to disease progression, thereby resulting in a shorter follow-up period for these patients. In both our study and in that by Nigro et al., it was found that a higher frequency of irADRs occurred in the early latency period rather than in the late one (9).

We also found that a high proportion of patients required some kind of pharmacological measure to treat their ADRs. In some cases, this was a permanent therapy replacement, as in the case of the endocrine irADRs. Such measures increase the complexity of patient management, in addition to resulting in a temporary or permanent interruption of their immunotherapy treatment. Furthermore, the need to administer corticosteroids in 21 (24%) patients and the necessity to interrupt treatment in 13 (15%) patients constitute lower numbers than those reported by Nigro et al., where 51 and 56% of patients suffering from early-onset irADRs and late-onset irADRs, respectively, required corticosteroid treatment, while 15.2 and 22% required their treatment to be interrupted (9). In our study, other pharmacological interventions for the treatment of diarrhoea, arthralgia, and other minor ADRs were also recorded, thereby resulting in higher percentages of patients receiving treatment.

The main strength of the present study is that it was specially designed to evaluate ADRs, and in particular, irADRs. The prospective nature of this study and the intensive monitoring of ADRs, along with the review of medical records and monthly phone calls to patients, allowed the comprehensive detection of ADRs. Moreover, the specific definition of an adverse reaction (11, 12) allowed us to rule out other concurrent events that were reported in previous studies. Furthermore, we systematically evaluated the causal relationships between the treatments employed and the suspected adverse reactions using the methods and algorithm provided by the Spanish Pharmacovigilance System (SEFV) (18). In addition, the long-term follow-up period and the specific attention paid to a variety of irADRs are expected to enhance our understanding of ADRs.

However, it should also be noted that some limitations can be found in our study. Firstly, it was a unicentric study, and the number of patients included was not sufficient to provide specific information related to each evaluated drug. However, a high percentage of the total cancer patients from throughout Catalunya attend our hospital. In addition, as the use of immunotherapy is increasing and the characteristics of treated patients may vary over time, the generalisability of our study could be affected. Furthermore, we did not evaluate combination therapies since the objective of this study was to monitor a unique active ingredient so as to avoid the contribution of other drugs when considering the attribution of causation. Finally,

TABLE 5 Management of adverse drug reactions.

n (%)	All ADRs* 353 (100)	Patients 75 (100)	irADRs 156 (100)	Patients 63 (100)
No intervention or hygienic-dietetic measures	199 (56.5)	68 (90.7)	94 (60.3)	50 (79.4)
Surgery treatment	3 (0.9)	3 (4.0)	1 (0.6)	1 (1.6)
Transfusion	3 (0.9)	3 (4.0)	0 (0)	0
Pharmacological measures**, *n* (%)	147 (41.7)	58 (77.3)	61 (39.1)	36 (57.1)
Analgesics	19	11	8	6
Antibacterials for systemic use	45	28	9	6
Antidiarrheals, intestinal antiinflammatory/antiinfective	15	10	15	10
Agents acting on the renin-angiotensin system	7	3	0	0
Antihistamines for systemic use	10	8	9	7
Antiinflammatory and antirheumatic products	7	5	5	3
Corticosteroids, dermatological preparations	11	7	10	6
Corticosteroids for systemic use	51	20	37	16
Diuretics	7	6	0	0
Drugs for obstructive airway diseases	6	3	0	0
Drugs for functional gastrointestinal disorders	9	8	1	1
Drugs for acid related disorders	5	4	0	0
Ophthalmologicals	12	5	3	2
Nasal preparations	5	4	3	2
Cough and cold preparations	5	5	0	0
Topical products for joint and muscular pain	5	3	4	3
Thyroid therapy	14	6	14	6
Others***	54	21	22	9

*Management was unknown in one ADR.
**Patients can be treated with one or more pharmacological measures; in 3 ADRs (1 patient) information on the specific drug was not available.
***See details of other therapeutic groups with a frequency less than 5 on Supplementary Table S2.

as mentioned above, we note that in a high proportion of patients, it was necessary to interrupt treatment due to disease progression, ultimately resulting in a short follow-up period for those patients.

Conclusion

In our prospective observational study carried out at the Vall d'Hebron University Hospital (Catalunya, Spain), the majority of cancer patients treated with immunotherapy (i.e., monotherapy of PD1/PDL1 (programmed death-ligand 1) checkpoint inhibitors) experienced adverse drug reactions (ADRs). Although most reactions were mild, 11.5% were categorised as grade 3 or above. In addition, a high percentage of the ADRs were immune-related ADRs (irADRs) that occurred at any time during treatment, and therefore the early identification of such reactions through the close monitoring of patients is recommended. Indeed, the real-world data reported herein emphasise the requirement for the strict monitoring and multidisciplinary management of irADRs due to the fact that they often require pharmacological interventions, or could even be life-threatening. It is also possible that such irADRs could affect the continuation of immunotherapy treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Vall d'Hebron Hospital Ethical Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MS, NG, M-JC, AF, EF, IB, JC, RM, and EM-C participated in the conception and design, interpretation of data, and writing the paper. EP participated in the conception and design, data analysis, interpretation of data, and writing the paper. XV

participated in the design and data analysis. AA participated in the conception and design, interpretation of data, writing the paper, and coordinated the whole project. All authors contributed to the review and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer FMV declared a shared affiliation, with several of the authors MS, XV, and AA at the time of the review.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.891179/full#supplementary-material

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The effects of glucocorticoids and immunosuppressants on cancer outcomes in checkpoint inhibitor therapy

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The emergence of checkpoint inhibitors has created a paradigm shift for the treatment of various malignancies. However, although these therapies are associated with improved survival rates, they also carry the risk of immune-related adverse events (irAEs). Moderate to severe irAEs are typically treated with glucocorticoids, sometimes with the addition of immunosuppressants as steroid-sparing therapy. However, it is unclear how glucocorticoids and immunosuppressants may impact cancer survival and the efficacy of immune checkpoint therapy on cancer. In this narrative review, we discuss the effects of glucocorticoids and immunosuppressants including methotrexate, hydroxychloroquine, azathioprine, mycophenolate mofetil, tumor-necrosis factor (TNF)-inhibitors, interleukin-6 inhibitors, interleukin-1 inhibitors, abatacept, rituximab, and Janus kinase inhibitors (JAKi) on cancer-specific outcomes in the setting of immune checkpoint inhibitor use.

KEYWORDS

checkpoint inhibitor therapy, glucocorticoids, immunosuppressants, cancer, immunotherapy

Introduction

Immune checkpoints are responsible for maintaining self-tolerance and preventing autoimmune disease in healthy individuals. However, in patients with cancer, tumor cells develop mechanisms that enhance these inhibitory pathways to evade an immune system response. Immune checkpoint inhibitors (ICIs) augment patients' immune responses by inhibiting these checkpoint pathways. These agents have had tremendous success slowing tumor progression and increasing overall survival in different cancer types. However, as ICIs inhibit mechanisms responsible for self-tolerance, they may also cause inflammatory and immune-related adverse events (irAEs) that can affect virtually any organ system and can be life-threatening (1, 2). Although the pathogenesis of irAEs is still being

understood, the activation of T-cells also increases the production of pro-inflammatory cytokines that are commonly seen in autoimmune diseases including interleukin (IL)-17, IL-21, and IL-6 (2).

The development of irAEs may indicate a greater immune response and could therefore be associated with improved tumor outcomes. Conversely, there is logical concern that treating irAEs with immunosuppressive agents may diminish the tumoral immune responses and negatively impact the efficacy of ICIs. This review summarizes the evidence on the use of different immunosuppressants for the treatment of irAE and their potential impact on overall survival and tumor responses in cancer patients receiving ICIs. As there is no data from clinical trials, our review is primarily based on observational studies and case series. It is important to note, that studies are difficult to interpret as irAEs have been shown to have better outcomes because of immune responses against tumors, however, irAEs may also potentially increase the risk of treatment-related morbidity and mortality, and their treatment with immunosuppressants could also impair tumor responses. In this review, we will discuss the effects of glucocorticoids, tumor necrosis factor (TNF)-inhibitors, and interleukin-6 inhibitors.

Glucocorticoids

Glucocorticoids are generally prescribed as first line treatment for irAEs as recommended by professional guidelines the American Society of Clinical Oncology and European Society of Medical Oncology guidelines (3–5). These agents have strong immunosuppressant effects, and their potential biologic impact on cancer appears to be multifaceted. Furthermore, their effects may vary according to the type of malignancy (6).

We review the available evidence on the general tumoral effects of glucocorticoid therapy in patients with cancer receiving these agents, in those who are already on glucocorticoid therapy for other disorders when they start ICI therapy, and in those who receive glucocorticoids for the treatment of irAE.

Use of glucocorticoids at onset or early on after initiating ICI therapy

There have been multiple recent studies and systematic reviews that have explored the effects of glucocorticoid therapy in general, on tumor progression and overall survival. A summary of relevant studies is shown in Table 1 (7, 10, 12, 16–18, 20, 21). These are mostly retrospective observational studies including patients who had been receiving an equivalent dose of prednisone of ≥10mg within the four weeks of initiation of ICIs for either irAEs, cancer-related symptoms, or other medical conditions such as chronic obstructive lung disease, autoimmune diseases, or radiation pneumonitis. These studies suggest that patients receiving glucocorticoids at baseline when receiving ICIs had decreased overall survival (OS) and progression-free survival (PFS) compared to those who did not receive glucocorticoids or received lower doses (9, 11, 17, 18). However, they did not adjust for reasons for baseline glucocorticoid use.

Patients receiving glucocorticoids when initiating ICI may have increased tumor burden or comorbidities, which are associated with decreased survival. Therefore, some studies have examined if the reasons for glucocorticoid use at baseline can explain differences in OS and PFS, as opposed to attributing these effects to solely to the interaction between glucocorticoids and ICIs. Results have been mixed. For example, one retrospective study in patients with non-small cell lung cancer receiving ICIs compared 38 patients that received baseline steroids for cancer-related symptoms, 11 that received steroids for other indications (including irAEs or comorbidities), and 299 who were steroid naïve. Patients receiving glucocorticoids for cancer symptoms had worse outcomes than those receiving them for irAE (HR 4.53, 95% CI 1.8-11), clearly showing that the indication for therapy is an important confounder (12). These findings have also been replicated in a smaller retrospective study in Sweden with 196 patients with non-small cell lung cancer that showed early glucocorticoid use within four weeks of ICI for irAEs did not appear to affect the efficacy of ICIs or OS (19). This study did confirm previous findings that baseline use of glucocorticoids for cancer-related symptoms was associated with decreased OS. A recently published systematic review including twelve randomized clinical trials showed that the administration of dexamethasone with chemotherapy and ICIs as part of treatment protocols to mitigate adverse events had improved OS than treatment arms that did not include dexamethasone (13). However, these results of cannot be generalized to patients who receive chronic daily steroids as it only included pre-treatment doses with infusions.

There is scarce and conflicting evidence on the effects of concomitant therapy with glucocorticoids when starting ICI on the subsequent efficacy of these agents. Future studies need to be carefully designed as decreased survival may be related to pre-existing comorbidities and advanced tumor burden in those patients' receiving glucocorticoids when initiating ICI. Furthermore, the current evidence is mostly confined to non-small cell lung cancer.

Use of glucocorticoids to treat irAEs

The associated effects of glucocorticoids on cancer outcomes when used for the treatment of irAEs is difficult to interpret. While glucocorticoids may mitigate the immune effects of ICIs, irAEs themselves may be a prognostic marker for enhanced tumor response to ICIs (15). Ideally, the comparison of outcomes between patients with the same irAEs treated with and without glucocorticoids in a clinical trial would provide more clarity but has obvious ethical considerations, as these agents are recommended as first-line treatment for irAE in

TABLE 1 Selected studies exploring the effects of glucocorticoids on cancer outcomes in the setting of immune checkpoint inhibitors.

Author	Year	Type of Study N: sample size	Cancer	Type of ICI	GC Start Date from ICI	GC Indication	Outcome	Summary of findings
Arbour 2018 (7) †	2011-2017	Retrospective N: 640	NSCLC	Single-agent PDL1	Within 30 days	Any	OS, PFS	GC associated with worse OS, PFS versus no GC. Adjustment for GC indication not performed.
Bruyère 2021 (8)	2007-2018	Retrospective N: 828	Any solid tumors	Anti PDL1 or CTLA-4	Any time	irAEs	OS, PFS	GC for irAEs associated with shorter PFS and OS – possibly mediated by interruption of ICI therapy.
Chasset 2015 (9)†	2010-2011	Retrospective N: 45	Melanoma	Ipilimumab	Within 30 days	Any	OS, ORS	GC at baseline associated with decreased OS. Analysis adjusting for GC indication not performed.
De Giglio 2020 (10)	2013-2018	Retrospective N: 413	NSCLC	All ICIs	Within 30 days	Any	OS, PFS	GC associated with worse OS if indication was for cancer symptoms but not for other reasons.
Drakaki 2020 (11)	2011-2018	Retrospective Claims N: 2213	NSCLC, Melanoma, Urothelial carcinoma	All ICIs	Within 30 days	Any	OS, TTNT	GC at baseline associated with worse OS in all three cancer types that persisted in multivariate models for NSCLC and urothelial cancer but not melanoma.
Fuca 2019 (12)†	2013-2017	Retrospective N: 151	NSCLC	All ICIs	Within 28 days	Any	OS, PFS	GC associated with decreased OS versus no GC. Analysis adjusting for GC indication not performed.
Li 2021 (13)	Search conducted November 2020	Systematic Review N=7155	NSCLC	Anti-PDL1	Pre-treatment with dexamethasone	Pre-treatment	OS, PFS	Pre-treatment with dexamethasone had improved PFS and OS. Pre-treatment was not associated with a lower rate of irAEs.
Maslov 2021 (14)	2014-2020	Retrospective N: 247	Any Metastatic Cancer	Anti-PD1/ PDL1	Any time	Any	OS, PFS, ORR	GCs within two months of ICI was associated with worse OS and PFS than GCs after two months. Comparisons were not made with non-GC groups.
Paderi 2021 (15)	2016-2020	Retrospective N: 146	NSCLC, melanoma, renal carcinoma	Nivolumab, atezolizumab, pembrolizumab	Any time	Any	PFS	GCs for irAEs within 30 days was not associated with decreased PFS. GC for irAEs after 30 days was associated with improved OS.
Petrelli 2020 (16)†	Search conducted June 2019	Systematic Review N: 4045	Any cancers	All ICIs	Any time	Any	OS, PFS	GC associated with worse OS and PFS if indication was for supportive care or cancer symptoms, however, not for irAEs.
Riudavets (17)	2013-2018	Retrospective N: 267	NSCLC	Anti-PDL1 with possible Anti-CTLA4	Any time	Any	OS	GC associated with worse OS when used for cancer-related symptom but decreased irAEs. No decrease in OS when GC use for irAEs versus no GC.
Scott 2018 (18)†	2015-2017	Retrospective N: 210	NSCLC	Nivolumab	Within first 30 days of ICI.	Any	OS	GC associated with worse OS versus no GC. Analysis adjusting for GC indication not performed.
Skribek 2021 (19)	2016-2019	Retrospective N: 196	NSCLC	All ICIs	Any time	Any	OS	GC for cancer symptoms associated with worse OS but not when given for irAEs
Svaton 2020 (20)	N/A*	Retrospective N: 224	NSCLC	Nivolumab	N/A*	Any	ORS	Baseline GC associated with worse ORS compared to non-GC. GC Analysis adjusting for GC indication not performed.
Tokunaga 2019 (21)	N/A	Retrospective	Melanoma	Ipilimumab	Any time	Any	OS	GC started within 7 weeks of ipilimumab was associated with worse OS than GC started after 7 weeks, in patients with low tumor mutation burden.

ICI, Immuncheckpoint inhibitors; GC, Glucocorticoids; NSCLC, Non-small cell lung cancer; OS, Overall Survival; PFS, Progression Free Survival; irAEs, Immune-related adverse events; ORS, overall response rate; TTNT, Time to next treatment; N/A, Not Available.
*Data could not be extracted as only abstract was available.
†Overlap between in publications included within the systematic review.

clinical practice guidelines (3–5). For many of the available studies there are biases that are difficult to adjust for, especially in the setting of smaller sample sizes and rare events. A systematic review published in 2020 explored the association of glucocorticoids use and survival in patients with irAEs (16). This review included 16 studies with 4,045 patients. All studies but one was retrospective with a mostly low quality of evidence. This review showed that patients taking glucocorticoids had an increased risk of death (HR 1.54, 95% CI 1.24-1.91). However, after performing a subgroup analysis for the use of glucocorticoids for irAEs (9 studies with 926 patients), the HR decreased to 1.08 (95% CI 0.79-1.49) suggesting that the use of glucocorticoids for irAEs may not affect OS.

Other studies have investigated if the timing of glucocorticoids for irAEs may affect overall survival (within 30 days of ICIs versus after 30 days). One study of 156 patients examined OS in patients who received glucocorticoids within 30 days or after 30 days of initiation ICIs for irAEs. This study showed no association in glucocorticoid use and overall survival and a possible improved outcome for those who started steroids after 30 days – although this is prone to immortality bias (15). A separate retrospective study including 257 patients who received steroids for irAEs showed decreased overall survival if glucocorticoids were initiated within two months of ICI onset after adjusting for glucocorticoid indication including tumor site, brain metastases, and the type of irAEs (14).

Overall, the current data suggests that the use of glucocorticoids for irAEs may not have a large deleterious effect on overall survival. However, one needs to consider that most patients with irAE receive glucocorticoids initially and that the development of irAE may be associated with better response to ICI, as it may indicate a more robust immune response (15). Some data suggests that early use of glucocorticoids (within 60 days of ICIs) may be associated with worse cancer outcomes, but further studies are needed to validate this finding. Recent data also suggests that this may also be due in part due to interruption or discontinuation of ICIs while patients have irAEs (8). Finally, glucocorticoids are used at varying dosages and durations depending on the type and severity of the irAE being treated. Studies have been too small to account for these differences.

Glucocorticoids continue to be the preferred first-line agent or moderate to severe irAEs. However, their effect on tumor responses is not well-characterized as most studies are retrospective and cannot account for the interactions between irAEs and improved tumor outcomes versus glucocorticoids and hampering of ICI effects. The current evidence suggests that patients who are receiving glucocorticoids at the onset of ICI therapy may have decreased survival, but that this effect may also be confounded by indication bias, as patients on glucocorticoids are likely to have more advanced cancer and worse performance status – this needs to be validated in well-controlled prospective studies.

The evidence on the use of glucocorticoids for irAEs was not robust but overall, glucocorticoids did not appear to have a large deleterious effect on overall survival – an exception might be use early on, within 60 days of initiating ICI therapy. An additional issue confounding the effect of glucocorticoid use for irAE is that patients who develop immunotoxicity are likely to discontinue ICI more often, or earlier compared to those without irAE. Therefore, observed deleterious effects on survival could be related to early discontinuation of ICI therapy. As most studies have been retrospective, larger, prospective studies are needed to adjust for various confounders and to better establish potential differences according to dose and duration of glucocorticoid therapy during treatment with ICI.

Conventional systemic disease modifying antirheumatic drugs and immunosuppressants

Glucocorticoids at the high doses that may be needed to treat irAEs can result in severe adverse events including infection, diabetes and cardiovascular disease among others. Also, because of the concern reviewed above on how their broad mechanism of action may impair the efficacy of ICI, there is a need for the use of steroid-sparing agents to be introduced early in the treatment of irAEs.

The use of conventional synthetic disease modifying antirheumatic drugs (csDMARDs) such as methotrexate or hydroxychloroquine has largely been confined to irAE arthritis and cutaneous disease. The csDMARDs have heterogenous mechanisms of actions that make it difficult to predict their potential interactions with ICI. In this section, we will discuss the use and of several csDMARD including methotrexate, hydroxychloroquine, azathioprine, and mycophenolate mofetil for the treatment of irAEs and their potential effect on ICI efficacy and tumor response.

In general, csDMARDs have not been associated with an increased risk for malignancy when used for the treatment of autoimmune diseases such as rheumatoid arthritis. An exception might be mofetil mycophenolate for which an association with lymphoma has been described in rare cases (22, 23).

Methotrexate is an immunomodulator that is frequently used in low doses for the treatment of inflammatory arthritis. Its proposed mechanism of action in rheumatoid arthritis is likely driven by adenosine signaling promoting an overall anti-inflammatory state. At low doses it is unlikely to cause critical immunosuppression. It has therefore been used widely in the treatment of irAE-arthritis (from CTLA-4, PD-1, or PD-L1 inhibitors alone or in combination) in patients in whom from glucocorticoids cannot be tapered successfully (24). Immune-related arthritis (from CTLA-4, PD-1, or PD-L1 inhibitors) responds well to methotrexate and does not seem to increase

cancer progression (25, 26). It is not currently known whether continuing treatment with methotrexate in patients with rheumatoid arthritis affects the outcomes of patients with concomitant cancer receiving ICI.

Hydroxychloroquine is an immunomodulator that is frequently used in the treatment of systemic lupus erythematosus. Hydroxychloroquine impairs the fusion of autophagosomes with lysosomes (autophagy) and has been shown to decrease inflammation and improve outcomes in lupus (27). Interestingly, this autophagy effect is currently being investigated in multiple cancer types to see if it can sensitize cancer cells to chemotherapy (28). Hydroxychloroquine has also been used successfully in the treatment of IR-arthritis (from CTLA-4 inhibitor and/or a PD-1/PD-L1 inhibitor) (29). As hydroxychloroquine is not an immunosuppressant it is unlikely that it may affect tumor progression or the efficacy of ICI, however, the evidence is currently scarce and further research is needed.

Other immunosuppressants such as azathioprine and mycophenolate mofetil have been used for severe irAEs. The use of azathioprine is mostly restricted to irAE hepatitis when steroid-sparing agents are needed, as recommended by guidelines (3–5). Mycophenolate mofetil has also been used in the setting of irAE hepatitis, colitis and myocarditis. The efficacy of these agents is largely limited to case series and reports. It is unknown how these agents may affect tumor progression in the setting of ICIs.

While csDMARDs and synthetic immunosuppressants might be useful in the management of irAE without compromising tumoral immunity, a major drawback is the delay in the onset of response which can take weeks or months. For this reason, there is interest in other therapies, such as biologic agents that may have a faster onset of action.

Biologic immunosuppressants

Several biologic agents targeting specific immune pathways and cytokines have been used in the treatment of irAE, most commonly tumor necrosis factor inhibitors (TNFi) and interleukin 6 inhibitors (IL6i).

Tumor necrosis factor inhibitors

TNFi have been widely used for the management of various irAEs (from CTLA-4, PD-1, and/or PD-L1 inhibitors) such as colitis, myositis and inflammatory arthritis (30).

The role of TNF in the pathogenesis of malignancy is mixed, with both pro-tumor and anti-tumor effects. The ability of TNF to invoke apoptosis in tumor cells is well-established. This led to a trial in the 1980s examined administering TNF directly to invoke tumor apoptosis (31). However, this induced severe systemic toxicity. Separate studies then demonstrated paradoxical results showing that increased levels of TNF may also predispose to the development of malignancies (32–34).

While there were initial reports suggesting that therapy with TNFi increased the risk of developing cancer, especially lymphoma, in patients with rheumatoid arthritis and other autoimmune diseases. However, recent studies have not confirmed this association (34, 35). Conceivably, patients with more severe autoimmune disease are more likely to receive these drugs, and high inflammatory states have been associated with increased risk of cancer, possibly confounding the earlier reported associations. There is scarce data on the use of TNFi for the treatment of autoimmune disease in patients with concomitant cancer. Most studies have not shown worse survival outcomes with this treatment, but in most cases TNFi were given to patients with a history of malignancy, or who had been several years in remission rather than to those with active cancer undergoing treatment (36, 37).

TNFi for the treatment of cancer

Because of the potential tumorigenic effects of TNF, a few trials have investigated the use of infliximab, a TNFi, for the treatment of advanced cancer (38, 39). While no major adverse outcomes were observed, there have not been other published studies reporting significant clinical benefits in the treatment of cancer.

TNFi in patients receiving ICI

Preclinical studies of TNF and TNFi show varying effects on cancer cells and cancer immunity, which adds to the complexity of how these agents may impact the efficacy of ICI when used to treat irAE (40). *In vitro* studies have suggested that the addition of TNFi may augment the response against tumors when combined with immunotherapy (41). This led to a phase 1 trial that evaluated the use of TNFi in combination with ICIs (CTLA-4 and PD-1 inhibitors combination) for the treatment of melanoma (42). This study showed a high overall response rate with certolizumab, a TNFi, in combination with ICIs with a good safety profile. It is currently not known whether the use of TNFi during ICI may lower the risk of irAEs, although pre-clinical data suggest it may (43).

Two separate studies have shown mixed results on the effects of TNFi on cancer outcomes in melanoma, when used to treat irAEs. The Dutch Melanoma Treatment Registry included 1,250 patients of which 65 received TNFi for irAEs related to PD-1 and/or CTLA-4 inhibitors (44). This study showed that patients who received TNFi for the treatment for steroid-refractory toxicity had increased mortality compared to those who received steroids only (HR 1.61, 95% CI 1.03-1.51). However,

this study did not adjust for specific irAEs (for example, patients receiving TNFi may be more likely to have colitis). A separate retrospective study of 27 melanoma patients who received infliximab for the treatment of immune-related colitis (with PDl-1 and/or CTLA-4 inhibitors) showed that cancer outcomes were not affected (45). An additional retrospective study of 327 patients with different malignancies that received ICIs included 35 patients receiving TNFi and glucocorticoids for colitis versus 44 that received glucocorticoids only. This study showed that those with colitis had improved OS compared to those without colitis regardless of whether treatment was with glucocorticoids only or with infliximab (46).

Interleukin-6 Inhibitors

Interleukin-6 (IL-6), an acute phase reactant, is a deleterious prognostic marker for melanoma, as increased levels are associated with decreased survival in patients with this disease (47, 48). Increased levels of IL-6 are observed in patients with cancer or autoimmune diseases, and also in cancer patients who develop immune toxicity from immunotherapy, chimeric antigen receptor-T (CAR-T) therapy, or ICI. Therefore, there has been an increased interest in the use of IL-6 inhibitors, such as tocilizumab or sarilumab, to treat irAEs, with the expectation that they will be efficacious in the treatment of irAEs, without any deleterious effects on cancer outcomes. IL-6 inhibitors have been extensively used in patients with rheumatoid arthritis, and there is no evidence that they increase the risk of developing malignancy (34, 35).

One case series of 22 patients treated with tocilizumab (two of whom started treatment prior to receiving ICI) demonstrated a good safety profile and efficacy for the treatment of irAEs in melanoma (related to PD-1, PD-L1, and/or CTLA-4 inhibitors) (49). A separate case series of 34 patients with mostly lung cancer and severe irAEs (from a PD-1 inhibitor only) also showed good therapeutic potential and safety profile of tocilizumab (50). However, cancer outcomes were not examined. A recently published systematic review examined cancer outcomes after therapy with tocilizumab for irAEs (51). The review included 31 studies (20 articles and 11 abstracts) with a total of 91 patients who received tocilizumab for irAEs. Cancer outcomes were reported in less than 20% of the cases. While there is a limited number of patients reported, there have been no reports of disease progression after starting tocilizumab (51).

IL-6 inhibitors appear to be a potentially promising treatment for irAEs that may not affect the efficacy of ICI. However, the literature is scarce and more evidence from prospective studies is needed.

Interleukin-1 inhibitors

Interleukin-1 (IL-1) is another cytokine that has been noted to be pro-inflammatory within the tumor milieu. The tumor microenvironment is typically pro-inflammatory, and inflammation is thought to instigate carcinogenesis and promote tumor growth and progression. Interleukin-1 potentially plays a key role in mediating these processes (52). A randomized controlled trial that examined the efficacy of canakinumab on atherosclerosis reported in an exploratory analysis that canakinumab potentially decreased the risk of lung cancer and improve lung cancer outcomes (53). The efficacy of anti-IL-1 therapy for cancer treatment is now being evaluated in various malignancies such as pancreatic, lung cancer, and melanoma among others (54). It is also being investigated as an adjunct therapy to ICI to potentially improve outcomes.

Interleukin-1 inhibitors are effective in the treatment of autoinflammatory diseases and gout, but are not used in other autoimmune diseases such as inflammatory arthritis or inflammatory bowel diseases. Some studies have shown that high levels of circulating IL-1 may be predictive of irAEs in melanoma (55). Therefore, there may be a role for IL-1 inhibitors in the treatment of irAEs as they are strong anti-inflammatory agents, and potentially could improve cancer outcomes. However, the current clinical data is scarce and more research is needed.

Abatacept

Abatacept is a modified antibody that contains the extracellular CTLA-4 domain and prevents the activation of T-cells. Abatacept has been widely used in autoimmune diseases such as rheumatoid arthritis and psoriatic arthritis. The mechanism of abatacept is directly contradictory to anti-CTLA4 checkpoint inhibitors such as ipilimumab. Therefore, there is concern that the use of abatacept would strongly inhibit the tumor effects of checkpoint inhibitors and has not been widely used. Furthermore, studies of patients with rheumatoid arthritis receiving abatacept have shown an increase in the risk of developing malignancies, especially melanoma (35, 56).

The evidence of abatacept in the treatment of irAEs is limited to case reports in the setting of life-threatening disease with myocarditis and myasthenia gravis. These have shown that abatacept may lead to the successful treatment in these patients (the two cases referenced include nivolumab and nivolumab/ipilimumab) (57, 58). However, cancer outcomes have not been explored and there is no other observational data. Due to the theoretical deleterious effects of abatacept on tumor progression, its use should likely only be reserved for patients with severe life-threatening disease.

Rituximab

Rituximab is a monoclonal antibody that targets CD20 to deplete B-cells. It used commonly in leukemia, lymphoma, and

autoimmune disease (such as vasculitis and rheumatoid arthritis). There is no clear evidence that rituximab increases the risk of developing other malignancies when used for these diseases. Rituximab has been used in combination with chemotherapy and ICI in lymphoma with favorable safety profile but unclear tumor benefit in this setting (59).

The interaction between rituximab and ICI is unclear and there is a paucity on knowledge at this time as to how the depletion of B-cells may interact with the effects of ICI on inhibitory pathways – though preclinical evidence seems to suggest that B-cell depletion does not have an effect on tumor response to ICI (60).

A case report of a patient who received rituximab for the treatment of vasculitis with complete depletion of B-cells, after receiving a PD-1 inhibitor she had adequate tumor response and tolerability (61). Another retrospective of 10 who received rituximab for the treatment of cutaneous irAEs all had an excellent response, but cancer outcomes were not reported (62).

Although rituximab is recommended as therapy for selected ICI in practice guidelines, there evidence is confined to case reports and small case series, with no information on how it may impact ICI efficacy and cancer outcomes.

Other biologic agents

There are other biologic agents targeting different cytokines (e.g IL-17, IL-23, IL-12 inhibitors) that are approved for use in patients with autoimmune disorders such as psoriasis, psoriatic arthritis, and ankylosing spondylitis. While their use for the treatment of irAE is of interest, as they target inflammatory cytokines, there is no evidence on their use other than in isolated case reports.

Targeted synthetic therapies: Janus kinase inhibitors

The Janus tyrosine kinase (JAK) pathways are crucial for intracellular signaling in inflammatory responses. Dysregulation of the JAK axis is thought to play a role in autoimmunity and oncogenesis (63). Several JAK-inhibitors (tofacitinib, upadacitinib, baricitinib, and others) have been successfully used in autoimmune diseases such as rheumatoid arthritis and psoriatic arthritis. However, a recent randomized safety controlled trial comparing tofacitinib and adalimumab, a TNFi, in patients with rheumatoid arthritis, showed an increased risk for the development of malignancy in patients receiving tofacitinib, not meeting the pre-established non-inferiority criterion (64). There is no data evaluating the safety of JAKi in patients with autoimmune disease and concomitant cancer.

JAK signaling contributes to the pathophysiology of irAEs by establishing and perpetuating a pro-inflammatory environment. The use of JAKi for the treatment of irAE has been largely confined to case reports and case series. While there is interest in the use of these agents, there is also a concern that JAK pathways are instrumental to promote ICI anti-tumor responses, through their role in cytokine signaling, for instance interferon (65, 66). Therefore, there is a theoretical concern that the use of these inhibitors may decrease the efficacy of ICIs. Further research is needed to determine this relationship.

Conclusion

In summary, the use of ICIs has created a paradigm shift in oncology and greatly improved cancer outcomes. However, their widespread use has also caused the emergency of irAEs. While irAEs may be associated with better oncologic outcomes due to enhanced immune activation, their treatment may impair immune tumoral responses. There is limited data on the potential tumor effects and safety of drugs used for the treatment of irAE. Glucocorticoids are the most recommended first-line agents but the data on their possible effects on cancer progression is conflicting, and confounded by tumor characteristics, comorbidities and dosage and duration of treatment which have not been adequately adjusted for in the available studies. The data for the most used steroid-sparing treatments (TNFi, and IL-6 inhibitors) is also scarce, but there have been no significant concerns on their use. However, large, prospective, well controlled studies, ideally randomized will be needed to determine the safety and efficacy of these agents for the treatment of irAE in patients with different tumors receiving ICI. Furthermore, more research is needed to determine if there may be any differences in the treatment of immunosuppression through different classes of ICIs (such as PD-1 and PD-L1 inhibitors versus CTLA-4 inhibitors).

Author contributions

The authors confirm responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation. All authors contributed to the article and approved the submitted version.

Conflict of interest

Author MS-A has received consultant fees from participation on advisory boards for Gilead, Avenue Therapeutics, ChemoCentryx. Current member of advisory board for Celgene. All activities unrelated to this work.

The remaining author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The diagnosis of immune-related pancreatitis disguised as multifocal lesions on MRI by endoscopic ultrasound-guided fine-needle biopsy: A case report

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Immune checkpoint inhibitor (ICI)–related acute pancreatitis (irAP) is a rare, potentially life-threatening immune-related adverse event. Whereas CT and MRI remain first-line diagnostic imaging modalities, more patients are presenting with atypical irAP as ICI use increases. To appropriately manage these events, it is important to catalog these presentations and provide comprehensive clinical, radiological, and pathological descriptions to guide evidence-based practice. Here, we present the case of a 66-year-old man with advanced lung adenocarcinoma who, after the fifth course of toripalimab, developed epigastric discomfort and elevated serum amylase and lipase. irAP was suspected, but MRI revealed atypical, multifocal pancreatic lesions. To exclude metastases, an endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) was performed. EUS revealed a slightly swollen pancreas with heterogeneous echoic signals and scattered hyperechoic areas in the parenchyma without an obvious mass. Histopathological examination of the FNB revealed retention of the normal lobular pancreatic architecture with focal acinar atrophy associated with a $CD8^+$ T lymphocyte-predominant infiltrate, further confirming the diagnosis of irAP. After starting glucocorticoids, his symptoms resolved, serum amylase and lipase rapidly decreased to normal, and the abnormal MRI features diminished. irAP can, therefore, present as multifocal lesions on MRI, and, when metastatic disease requires exclusion, EUS-FNB is an effective way to establish a definitive diagnosis. Refining the histopathological and immunopathological criteria for the diagnosis of irAP is now warranted.

KEYWORDS

endoscopic ultrasound-guided fine needle biopsy, immune checkpoint inhibitor, pancreatitis, programmed death-1 antibody, immune-related adverse events

Introduction

Immunotherapy has dramatically revolutionized the therapeutic landscape for patients with cancer. Immune checkpoint inhibitors (ICIs) are now widely used in cancer management and include anti–programmed cell death protein 1 (PD-1) or anti–programmed cell death ligand 1 (PD-L1) inhibitors and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors. However, it also introduces a novel class of toxicity, termed immune-related adverse events (irAEs). IrAEs range from self-limiting to life-threatening, leading to their temporary or permanent discontinuation and consequent life-threatening tumor progression. Therefore, the early diagnosis and effective treatment of irAE are clinically imperative to maximize the utility of immunotherapies.

ICI-related acute pancreatitis (irAP) is a rare yet serious irAE, with a reported overall incidence of 1% across all drug types (1). However, the incidence of irAP is growing as ICI use becomes more common. Classical irAP presents as diffuse peripancreatic enlargement, decreased enhancement, and fat stranding similar to autoimmune pancreatitis (AIP) on computed tomography (CT) and magnetic resonance imaging (MRI). However, these radiological features may be variable, even absent, creating diagnostic uncertainty as ICI use increases (2). Understanding the spectrum of radiological and pathological features is important to aid clinical decision-making in terms of further investigations and management. Here, we report a case of irAP presenting with multifocal lesions on MRI, with endoscopic ultrasound (EUS) revealing no evidence of a mass and histopathological examination of the fine-needle biopsy (FNB) confirming the diagnosis of irAE. Presenting this case provides an opportunity to improve our understanding of atypical irAP and its radiological and pathological manifestations in the ICI era.

Case presentation

A 66-year-old man with left lung adenocarcinoma (cT1cN0M1b, stage IVb; *EGFR*, *ALK*, *BRAF*^{V600E}, *ROS1*, and *KRAS* mutation negative, PD-L1 unknown) had participated in a clinical trial studying standard-of-care pemetrexed and carboplatin with anti–PD-1 toripalimab therapy or placebo. While his disease initially stabilized, he later developed the progressive disease while on anti–PD-1/placebo monotherapy maintenance, and unblinding of the clinical trial indicated that he was in the placebo group. He was then started on toripalimab 240 mg every 3 weeks. After two courses of anti–PD-1 therapy, he achieved a partial response.

He developed epigastric discomfort after the fifth course of toripalimab, and physical examination revealed middle upper abdominal tenderness. The complete blood count and the liver/kidney/lipid panel were all within normal ranges. Serum amylase and lipase were raised [617 U/L (35–135 U/L) and 1,501 U/L (2–53 U/L), respectively]. High-sensitivity C-reactive protein and IgG4 were 2.77 mg/L (<3 mg/L) and 468 U/L (80–1,400 U/L), respectively. Peripheral blood T lymphocyte subset analysis showed only a $CD8^+HLA\text{-}DR^+/CD8^+$ T-cell ratio increase to 56.2% (6.3%–23.8%), whereas the $CD4^+$ T-cell, $CD8^+$ T-cell, $CD4^+/CD8^+$, and $CD8^+HLA\text{-}DR^+/CD8^+$ ratios were all within the normal range.

The pancreatic morphology was unremarkable on abdominal contrast-enhanced CT (CECT), with homogeneous pancreatic parenchymal enhancement. MRI revealed multiple, nodular, patchy areas of abnormal signal intensity within the pancreas: slightly hypointense in T1-weighted images (T1WI), slightly hyperintense in T2-weighted images (T2WI), and significant diffusion restriction on diffusion-weighted imaging (DWI). There were two prominent lesions with blurred margins in the pancreatic head and tail accompanied by segmental stenosis of the main pancreatic duct (MPD). Furthermore, dynamic contrast-enhanced MRI showed heterogeneous enhancement of the pancreatic parenchyma, with relatively higher enhancement in the pancreatic body and tail in the arterial phase. The pancreatic head showed only slight hyper-enhancement, and no significant abnormal enhancement was observed in the delayed phase (Figures 1A–C).

Because the lesions were multifocal, it was necessary to differentiate between metastases and irAP. Therefore, EUS-FNB was performed. On EUS, the pancreas was slightly swollen, and the echoic signals were slightly heterogeneous with scattered, striped hyperechoic areas in the parenchyma without obvious masses; the pancreatic tail was slightly enlarged (Figures 2A–D). An EUS-guided FNB of the pancreatic tail was taken with 19G needles (Expect, Boston Scientific, USA), fanning technique, and 5-ml suction by one needle pass. Histopathological examination of the needle core biopsy showed retention of the normal lobular architecture with focal acinar atrophy associated with a neutrophil and lymphocyte predominant infiltrate (Figures 2E, F) but no fibrosis. On immunohistochemical analysis, the lymphocytes were predominately $CD8^+$ T cells ($CD8^+ > CD4^+$), although scattered B cells were seen (Figures 2G–J). There was no increase in $IgG4^+$ plasma cells. The ductal epithelium was generally well preserved and was not associated with neutrophils. Immunohistochemical stains with antibodies targeting thyroid transcription factor 1 (TTF-1), IgG, and IgG4 were negative.

The patient was diagnosed with moderate irAP (grade 2), and he was treated with oral prednisolone 40 mg daily (0.7 mg/kg/day) with regular tapering of 5 mg every 2 weeks. His symptoms quickly settled, and his serum amylase and lipase had returned to normal 1 month later. Magnetic resonance cholangiopancreatography (MRCP) showed a decrease in the nodular and patchy abnormal signals, especially in the pancreatic body and tail (Figures 1D, E). The segmental

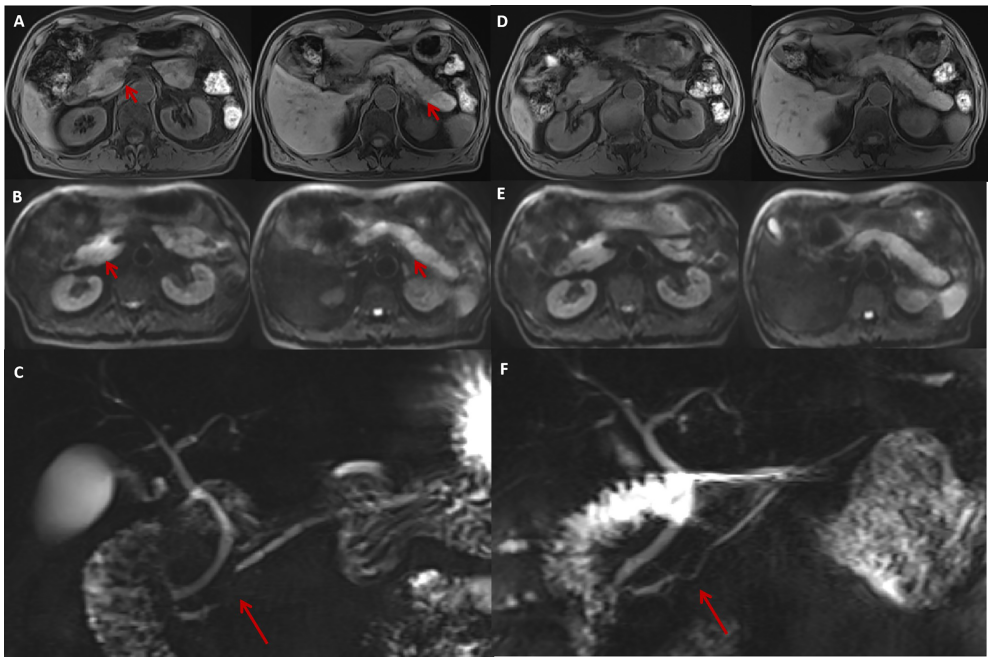

FIGURE 1
The MRI features of irAP and its improvement after treatment. The MRI at diagnosis revealed a slightly swollen pancreas with multiple nodular (**A**, arrow) and patchy abnormal signals with decreased intensity on T1WI sequences **(A)** and increased intensity on DWI (**B**, arrow) located in the pancreatic head and tail. MRCP showed segmental stenosis of the MPD in the pancreatic head (**C**, arrow). After 1 month of prednisolone treatment, the swelling reduced and the abnormal signals decreased on T1W1 **(D)** and DWI **(E)** sequences. The MPD stenosis also resolved (**F**, arrow). irAP, immune-related acute pancreatitis; MRI, magnetic resonance imaging; T1W1, T1-weighted image; DWI, diffusion-weighted imaging; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography.

stenosis of the MPD resolved with the consequent resolution of the distal MPD dilation (Figure 1F).

Discussion and conclusion

irAP is more common with CTLA-4 inhibitors than PD-1 inhibitors, and the incidence is reported to be additive with a higher risk in patients with combined therapies (3). Although less common, our patient developed irAP with anti–PD-1 monotherapy toripalimab. IrAP-related imaging studies are scarce, with the most comprehensive series describing the CECT and MRI features in 25 irAP patients, typically diffuse (56%) or focal (44%) acute interstitial pancreatitis; no patient had a pancreatic tissue biopsy (4). There are even fewer reports of the EUS and pathological features of irAP. Here, we present a case of irAP presenting with multifocal lesions on MRI, with EUS-FNB helping to establish the definitive diagnosis and exclude primary or metastatic malignancy through histopathological analysis.

For patients with suspected irAP, National Comprehensive Cancer Network (NCCN) guidelines recommend abdominal CECT as the first-line examination. However, we and others have found that the CECT plays only a limited role in the diagnosis of irAP, with a sensitivity of only 17%. MRI is sensitive for detecting pancreatic abnormalities, especially when CECT is inconclusive (5). In our case, T1WI sequences showed slightly decreased signal intensity, whereas DWI demonstrated significant diffusion restriction resembling AIP and different from acute edematous pancreatitis. Our patient also had segmental MPD stenosis with secondary distal MPD dilatation, which is more suggestive of AIP and consistent with a previous case report (6).

The multifocal lesions seen on MRI in our case were unusual and initially caused diagnostic uncertainty. In patients with pre-existing malignancy, excluding metastases is essential, and EUS is a very useful diagnostic modality in this regard. Previous reports of EUS in irAP are extremely rare, with only two cases showing typical diffuse hypoechoic pancreatic enlargement with scattered hypoechoic areas and patchy and heterogeneous parenchyma, and another case revealing a hypoechoic mass in the pancreatic neck causing MPD stenosis (6–8). In our case, the pancreas was slightly swollen, and, in contrast to CECT and MRI, no obvious mass was seen on EUS. MRI is generally considered a sensitive method for detecting inflammatory changes in the pancreas, and heterogeneous inflammation can

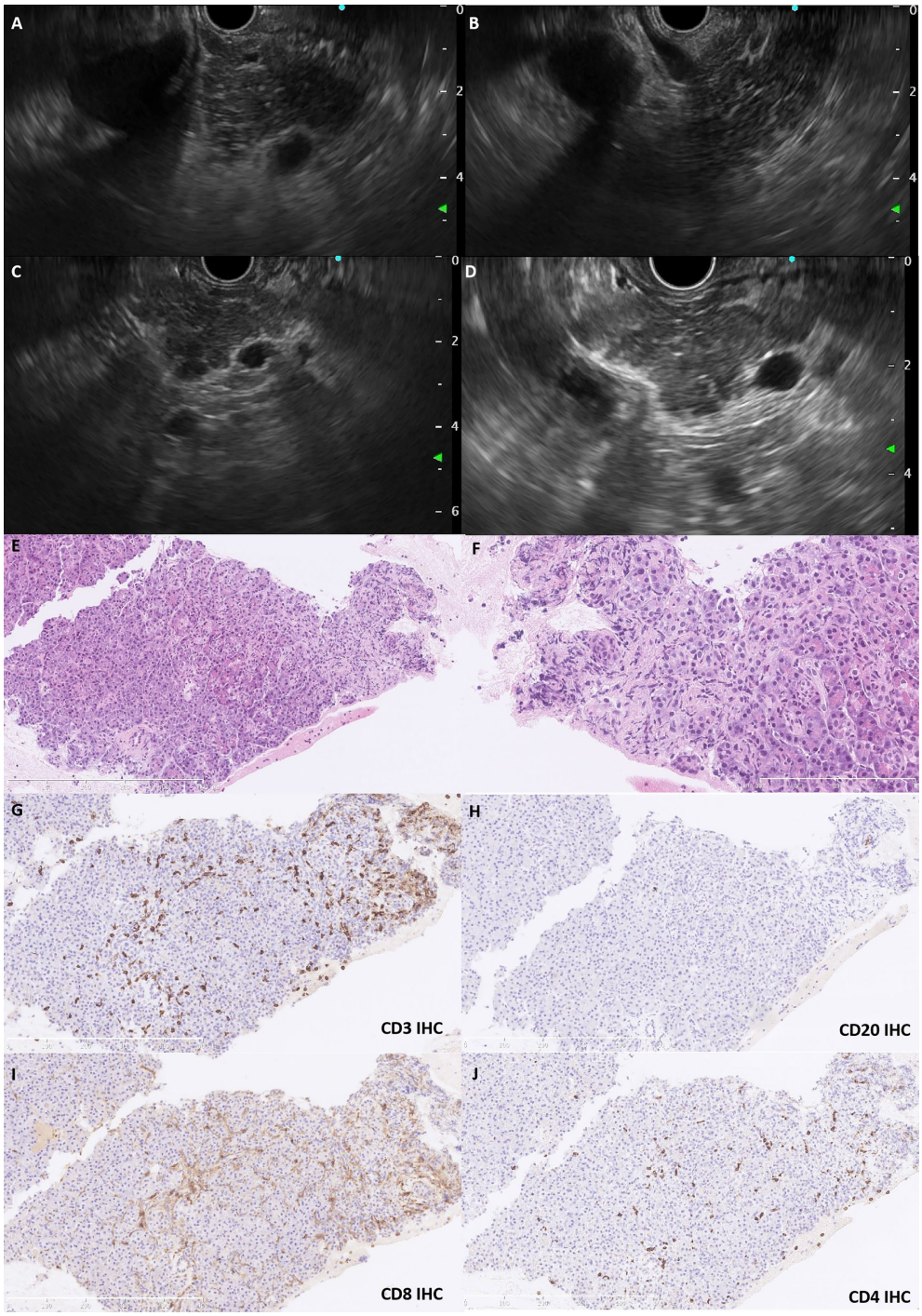

FIGURE 2
The EUS and histopathological features. EUS revealed a slightly swollen pancreas with heterogeneous echoic signals and scattered hyperechoic strips in the parenchyma **(A, B)**. The pancreatic duct was regular without dilatation, and the pancreatic tail was slightly enlarged without a mass lesion **(C, D)**. Pancreatic biopsy shows retention of the lobular architecture with focal atrophy of acini infiltrated with neutrophils and lymphocytes (**E**, HE staining,×150; **F**, HE staining, ×400). The lymphocytes were predominately T cells (**G**, CD3 IHC), although scattered B cells (**H**, CD20 IHC) were also present. $CD8^+$ T cells (**I**, CD8 IHC) tended to dominate compared with $CD4^+$ counterparts (**J**, CD4 IHC). EUS, endoscopic ultrasound; IHC, immunohistochemistry; HE, hematoxylin–eosin.

produce the appearance of multifocality on MRI. EUS is particularly sensitive for detecting masses, and even early-stage pancreatic carcinoma is more readily detected by EUS than CECT or MRI. Therefore, EUS is particularly useful for excluding space-occupying lesions and has the advantage that EUS-guided FNB can be used to obtain tissue to make a histopathological diagnosis, with 67% histologic capability and 93% accuracy (7). Because a false-negative result is possible through inadequate or unrepresentative tissue sampling, a final diagnosis might need to be confirmed by disease resolution with active management.

There are only two previous reports describing the cytopathological features of irAP, in which the inflammation was neutrophil-predominant (8, 9). Ours is the first case to describe the histopathological features of irAP, an analysis enhanced by immunophenotyping to establish the immune repertoire. We found that the pancreatic architecture was largely preserved, and neutrophils and lymphocytes infiltrated the pancreatic parenchyma but not the ductal epithelium. Type 2 AIP and other forms of chronic pancreatitis can have neutrophilic infiltrates within acinar units, but they often form microabscesses within duct lumina, which were absent in our case. In addition, the typical fibrosis seen in type 2 AIP was not present. Furthermore, both serum and tissue were negative for IgG4, which is a useful differentiation marker for type 1 AIP. An inflammatory infiltrate dominated by CD3+ T lymphocytes and a higher CD8+/CD4+ ratio can also support irAE and is consistent with the T-cell profile seen in a case of ICI-associated diabetes mellitus (10).

Our observations prompted us to speculate about the possible pathobiology of irAP. Anti–CTLA-4– and anti–PD-1–induced colitis have distinct immunological characteristics, with CD8+ and CD4+ T lymphocytes predominating in anti–PD-1– and anti–CTLA-4–induced colitis, respectively (11). In the case of pancreatic islet injury caused by combined anti–CTLA-4 and anti–PD-1 therapy, the low expression of PD-L1 indicated that β-cell injury was mainly associated with anti–PD-1 therapy, and the infiltrate was also CD8+ T cell–enriched, suggesting that CD8+ T-cell infiltrates are a more general feature of anti–PD-1 therapy. Immunophenotyping of T cells in pancreatic tissue biopsies may be useful for making the diagnosis of irAP, and further studies are now required to refine the diagnostic pathology criteria for irAP.

Interestingly, EUS also revealed scattered hyperechoic strips in the pancreatic parenchyma, which are a feature of early-stage chronic pancreatitis. Previous reports have shown that pancreatic atrophy developed in 11 of 25 (44%) irAP patients, and our previous study found that irAP can run a protracted course after glucocorticoid treatment (3, 5). IrAP has a tendency to become chronic and result in exocrine/endocrine insufficiency with a median 43% decrease in pancreatic volume (4, 10). Activated and increased CD8+ T cells damage pancreatic cells, further decreasing the number of pancreatic ductal and acinar cells to produce pancreatic atrophy (1). However, the imaging in the current case only suggested a sign of early pancreatic atrophy, and further studies are warranted to elucidate the pathophysiology and long-term progression of irAP (10).

This patient was diagnosed with moderate irAP; hence, the ICI was discontinued, and oral prednisolone 0.5–1 mg/kg/day was administered. Although Abu-Sbeih et al. found that intravenous fluids can potentially be beneficial to prevent long-term adverse outcomes from irAP (3), this was a retrospective study with a small sample size. Furthermore, 18 of 32 patients received only intravenous fluids without steroids suggesting mild disease and consistent with their excellent outcomes. In those patients with long-term adverse outcomes, 6 of 11 patients had neither intravenous fluids nor steroids, so the lack of active management may have played a role in these poor outcomes. Therefore, we gave glucocorticoid therapy without intravenous fluids to our patient with moderate irAP according to NCCN guidelines and our previous study (5), with good effect. Our patient still has a stable disease, but the resumption of an ICI can be considered if the tumor progresses.

In conclusion, irAP can present as multifocal lesions on MRI. In such cases, EUS is useful for distinguishing mass lesions from heterogeneous inflammation and to obtain tissue for histopathological examination. Histologically, irAP can show a relatively normal lobular pancreatic architecture with neutrophils, a CD8+ T lymphocyte predominance, and only scattered B cells without excess IgG4 plasma cells. Therefore, EUS-FNB is a helpful procedure for establishing the diagnosis of irAP, particularly when multifocal on traditional imaging, by excluding metastatic masses and establishing a definitive histopathological diagnosis.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

WS: clinical information collection, draft of the manuscript, and case discussion. YL: histopathological information collection and analysis, histopathological figures selection, and case discussion. LZ: radiological information collection and analysis,

radiological figures selection, and case discussion. YF: performing EUS-FNB and EUS figure selection and case discussion. QJ: guidance on EUS-FNB and EUS figure selection and case discussion. BT: clinical information collection, case discussion, refining the manuscript, and financial support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Myocarditis and myositis/myasthenia gravis overlap syndrome induced by immune checkpoint inhibitor followed by esophageal hiatal hernia: A case report and review of the literature

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Immunotherapy with programmed death 1 (PD-1) inhibitor has shown activity as first- or second-line treatment for various metastatic human malignancies. Immune-related adverse events (irAEs) are now well-described, and most organ sites are potentially influenced, but the prevalence of myocarditis and myositis/myasthenia gravis (MG) overlap syndrome following esophageal hiatal hernia induced by immunotherapy is rarely reported. Here, we describe a 71-year-old woman with a progressed unresectable extrahepatic cholangiocarcinoma and biliary obstruction. She had no prior history of muscle weakness and neuromuscular disease with a normal body mass index. She was treated with sintilimab as a rescue regimen of immunotherapy. After the first cycle of treatment, she experienced a grade 4 myopathy including simultaneous myositis, myalgia, and myocarditis due to multiple injuries in her cardiac, skeletal, and ocular muscles. She had elevated levels of creatine kinase (CK), cardiac troponin I, and myoglobin (MYO), but MG and myositis-specific and myositis-related antibodies were negative. Immunotherapy was discontinued and pulse high-dose methylprednisolone with a slow tapering and intravenous immunoglobulin (IVIG) was initiated. Two weeks later, the patient's clinical presentation improved significantly. A subsequent cardiac magnetic resonance (MR) examination revealed an old myocardial injury that may be a result of immune-related cardiac toxicity.

In the third month following the PD-1 inhibitor therapy, she restarted systemic chemotherapy in combination with an anti-angiogenic agent but without immunotherapy. Half a year later, she complained of repeated abdominal distension and radiographic examinations and endoscopy showed a clinically confirmed diagnosis of sliding hiatal hernia of the esophagus and gastroesophageal reflux disease. Due to mild symptoms associated with gastroesophageal reflux, she was suggested close monitoring with acid secretion blockade rather than immediate surgical intervention. The severity for patients with myositis and myocarditis accompanied without MG is similar to those with MG. Considering the use of PD-1 inhibitors is increasing in cancer patients, physicians should therefore pay more attention to immunotherapy-induced myocarditis with myositis/MG overlap syndrome. Since we hypothesize diaphragmatic hiatal hernia as a potential consequence of immunotherapy-induced myositis, reports on hiatal hernias subsequent to immunotherapy-induced myositis are needed.

KEYWORDS

PD-1 inhibitor, esophageal hiatal hernia, myositis, immune-related adverse event, myocarditis, myasthenia

Introduction

As a novel class of anti-tumor agents, immune checkpoint inhibitors (ICIs) targeting the interaction between programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) represent a major paradigm shift in cancer treatment. The use of ICIs such as PD-1 and PD-L1 inhibitors has been approved by Food and Drug Administration (FDA) and the National Medical Products Administration (NMPA) of China for treating many solid tumor types including melanoma, non-small cell lung cancer, small cell lung cancer, bladder cancer, and colorectal cancer (1). Although these drugs have shown impressive anti-tumor efficacy, they may be associated with a wide range of mild to severe or life-threatening characteristic adverse effects, termed autoimmune immune-related adverse events (irAEs). The most common irAEs occur in the skin, endocrine system, pulmonary, and gastrointestinal tract. The irAEs affecting the musculoskeletal system, cardiovascular system, and nervous system are relatively rare (2, 3). Myopathy induced by ICIs represents a multifaceted entity with diverse clinical features of the neuromuscular system, including myositis, myocarditis, general myasthenia, myasthenia gravis (MG), rhabdomyolysis, and dermatomyositis (4). Overlapping myositis with myocarditis, myasthenia, and ocular myositis has been reported in some literature (5, 6). However, only a few cases involved immune-mediated direct or indirect damage in the diaphragm (7). Here, we reported a rare case with extrahepatic cholangiocarcinoma who developed esophageal hiatal hernia resulting from clinically confirmed myositis accompanied by myocarditis and myasthenia after discontinuation of immunotherapy and steroid treatment, supporting the evidence of more generalized muscle involvement underlying clinical presentations. The severity for patients with myositis and myocarditis accompanied without MG is similar to those with MG. Physicians should therefore pay more attention to immunotherapy-induced myocarditis with myositis/MG overlap syndrome. Since we hypothesize diaphragmatic hiatal hernia as a potential consequence of immunotherapy-induced myositis, reports on hiatal hernias subsequent to immunotherapy-induced myositis are needed.

Case description

Ethical approval: The study was approved by the First Affiliated Hospital of Shandong First Medical University (No: [2022]-S479). Written informed consent was obtained from the patient. Written informed consent was obtained from the participant for the publication of this case report (including all data and images).

In August 2020, a 71-year-old Chinese woman was initially diagnosed with unresectable extrahepatic cholangiocarcinoma and biliary obstruction. She received an endoscopically implantable stent and six cycles of first-line chemotherapy with gemcitabine and cisplatin with tolerated chemotherapy-related adverse effects from September 2020 to April 2021. Unfortunately, in April 2021, she switched to immunotherapy with PD-1 inhibitor sintilimab due to disease progression. A week later after immunotherapy, the patient developed fatigue and low back pain without any treatment. In

May 2021, she began to suffer from limited movement, weakness, and soreness in the bilateral lower extremities that was accompanied with both eyelid ptosis, red to amber-colored transparent urine, and mild dyspnea (**Figure 1A**). This patient had no prior history of muscle weakness and neuromuscular disease with a normal body mass index of 20.2 kg/m^2. No abnormality was found in electromyography, and only multiple ischemic infarcts were found in brain magnetic resonance (MR). The electrocardiogram showed ectopic heart rhythm and atrial arrhythmia (**Figure 1B**). She had a right pleural infusion (**Figure 1C**). The echocardiogram showed an left ventricular ejection fraction (LVEF) of 65% with normal left ventricular systolic and diastolic functions. Subsequent screening for MG antibodies showed negative ryanodine receptor antibody (RyR-Ab) and weakly positive acetylcholine receptor antibody (AChR-Ab, 0.93 nmol/l, normal range <0.45 nmol/l). All myositis-specific and myositis-related antibody profiling revealed negative antibodies. Laboratory examinations showed that creatine kinase (CK) was increased to 1,658 U/L (normal range <140 U/L), creatine kinase isoenzyme (CK-MB) to 124.49 U/L (normal range <25 U/L), cardiac troponin I (cTnI) to 2.35 ng/mL (normal range <0.034 ng/mL), and myoglobin (MYO) to 965.4 ng/mL (normal range <61.5 ng/mL) (**Figure 2A**). She also had an elevated alanine aminotransferase (ALT) level of 309.1 U/L (normal range <40 U/L), aspartate aminotransferase (AST) level of 154.9 U/L (normal range <35 U/L), and lactate dehydrogenase (LDH) level of 1,616 U/L (normal range <214 U/L), but her brain natriuretic peptide (BNP) was normal (**Figure 2B**). At that time, she failed to conduct the cardiac MR examination and endomyocardial biopsy due to her poor performance status and discomfort symptoms. She also refused to do further muscle biopsy at that time. Based on the clinical manifestations and laboratory test results, a clinical diagnosis of grade 4 ICI-induced myopathy, including myositis, myalgia, myasthenia, and myocarditis due to multiple muscle injuries in cardiac, skeletal, and ocular muscle, was made. However, immune-related MG was ruled out. She was subsequently initiated with pulse methylprednisolone at 500 mg/d and for 5 days with gradually decreasing doses and intravenous immunoglobulin (IVIG) at a dose of 0.4 g/kg/d for 5 days. A week later, she still complained of bilateral eyelid ptosis, but weakness and soreness in the bilateral lower extremities were significantly improved. At that time, tacrolimus at 3 mg/d was added. After 2 weeks of pulse methylprednisolone treatment, all her clinical symptoms associated with immune-related myopathy improved significantly with gradually declining biochemical biomarker levels and she was discharged. A computed tomography (CT) scan showed a temporary right pleural effusion and a slight elevation of BNP (**Figures 1C**, **2B**). She was continuedly administrated with oral prednisolone at 60 mg/d for 4 weeks with a slow tapering for an additional 4 weeks (**Figure 3**). Because the patient's performance status improves significantly, 3 months after the onset of immune-related irAEs, she received a supplementary cardiac MR examination revealing no edema and hyperemia, and quantitative myocardial T1 mapping was normal (**Figure 1D**). Delayed myocardial enhancement showed patchy enhancement that may be old myocardial injuries resulting from immune-related cardiac toxicity (**Figure 1E**).

In the third month following the PD-1 inhibitor treatment, all symptoms associated with immune-related myopathy disappeared, including weakness in the bilateral lower extremities, soreness, and bilateral eyelid ptosis, and all biochemical biomarkers were normal. CT scan showed her right pleural effusion improved completely (**Figure 1C**). She discontinued immunosuppressive agents and oral prednisolone and was treated with systemic chemotherapy in combination with an anti-angiogenic agent but without immunotherapy. In January 2022, the patient complained of repeated upper abdominal distension for several days. CT scan for the first time showed abdominal viscera protruding into the left hemithorax (**Figures 4A,B**), and an esophageal hiatal hernia was suspected. Further upper gastroenterography and endoscopy showed no esophagitis and inflammation of the gastric body and antrum (**Figure 4C**), but a clinically confirmed diagnosis of sliding hiatal hernia of the esophagus (type I) was made (**Figure 4D**). A gastrointestinal motility examination confirmed a diagnosis of gastroesophageal reflux disease. Because this patient had only mild symptoms associated with gastroesophageal reflux, she was suggested close monitoring with acid secretion blockade rather than immediate surgical intervention.

Discussion

Immune checkpoint inhibitor-induced myopathy is characterized as a multifaceted entity with diverse clinical features of the neuromuscular system including myositis, myocarditis, myasthenic crisis, rhabdomyolysis, and dermatomyositis (4). Symptoms related to ICI-induced myopathy range from mild to severe toxicities, but the diagnosis of immune-related myopathy is often challenging because they may manifest as common symptoms such as cancer or other concurrent anti-tumor agent-related fatigue and weakness (4). The incidence of immune-related myocarditis is less than 1%, and most cases happen after initial one to two doses of ICIs and rapidly deteriorate, although some are asymptomatic with the elevation of cardiac marker levels alone. The incidence and mortality of myocarditis with cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitor in combination with PD-1/PD-L1 inhibitor is higher than those with PD-1/PD-L1 inhibitor alone (8). A recent review article demonstrates that MG is the most common ICI-related neuromuscular adverse effect (26.8%), followed by myositis (25.6%), and Guillain–Barre syndrome (18.3%) (9). ICI-induced myositis often has a broad spectrum, ranging from mild symptoms to

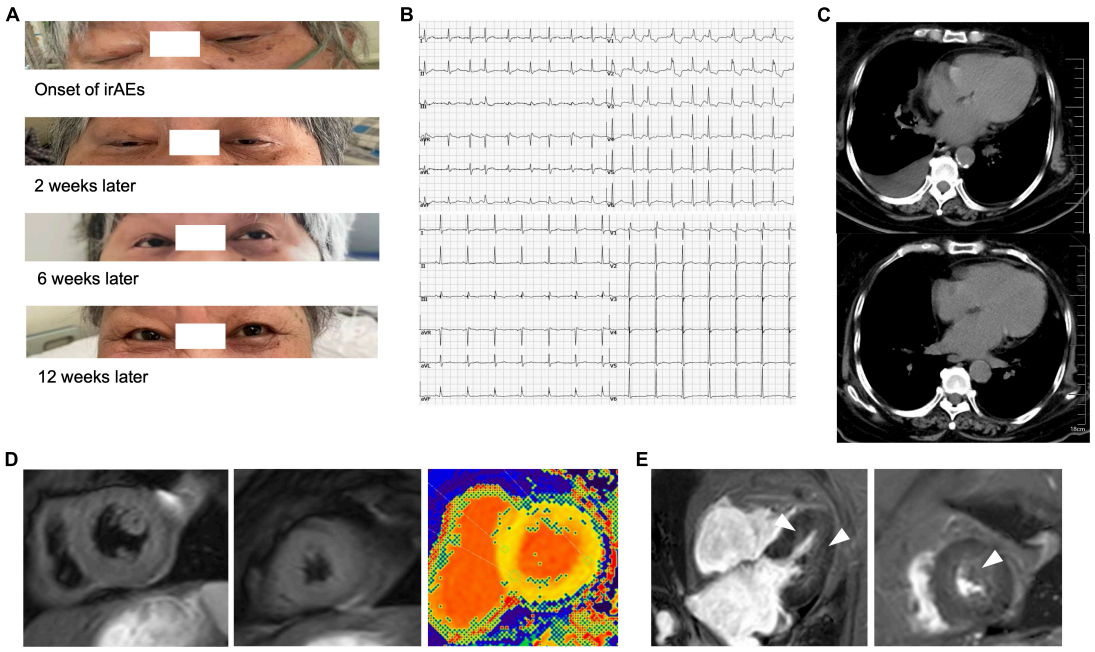

FIGURE 1
Eyelid ptosis and radiographical presentations of immune-related myocarditis. **(A)** Both eyelid ptosis occurred at the time of immune-related adverse events (irAEs) onset and improved gradually after the steroid treatment and intravenous immunoglobulin (IVIG). **(B)** The electrocardiogram showed ectopic heart rhythm and atrial arrhythmia before (upper) and after (lower) the steroid treatment. **(C)** Temporary right pleural infusion before (upper) and after (lower) the steroid treatment by CT scan. **(D)** In the third month after the onset of irAEs, the patient received a supplementary cardiac magnetic resonance (MR) examination revealing no edema and hyperemia (left and central), and quantitative myocardial T1 mapping was normal (right). **(E)** Delayed myocardial enhancement showed patchy enhancement that may be old myocardial injuries resulting from immune-related cardiac toxicity (arrow).

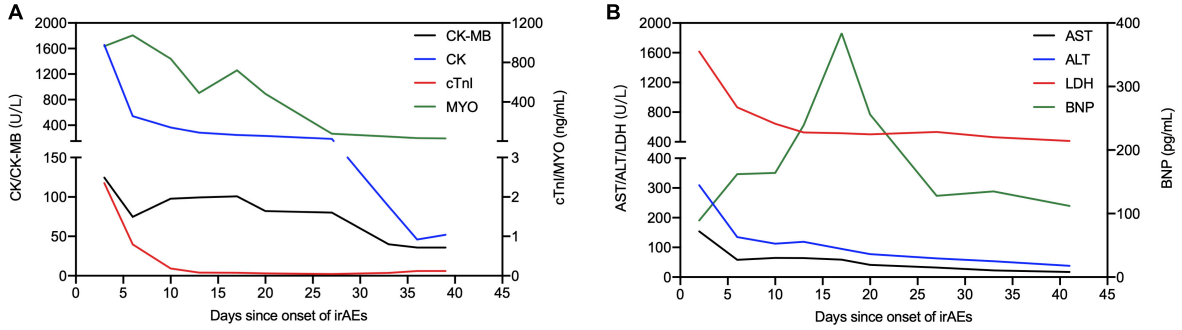

FIGURE 2
Illustration of main laboratory markers and steroid treatment following the onset of irAEs. **(A)** Dynamics of cardiac markers [creatine kinase (CK), creatine kinase isoenzyme (CK-MB), cardiac troponin I (cTnI), and myoglobin (MYO)]. **(B)** Dynamics of other biochemical markers [alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and brain natriuretic peptide (BNP)].

severe or life-threatening complications (10). Based on the pharmacovigilance database of the World Health Organization, Allenbach et al. (10) identified 465 cases of myositis with a total incidence rate of <1%. Among rheumatic irAEs (arthritis, myositis, sarcoidosis, Sjogren's syndrome, scleroderma, and rheumatic polymyalgia), myositis has the shortest median onset time (median 31 days; range 19.2–57.8) and the highest case fatality rate (24%), especially when it is associated with myocarditis (57%) (10). In Pathak et al.'s (11) study, most cases developed myositis symptoms after one ICI treatment. Compared with primary multiple autoimmune myositis (12), most cases progress rapidly. Elevated CK levels were reported in all cases. Based on VigiBase analysis (13), in 180 patients with myositis associated with ICI treatment, the mortality rate was significantly higher than that of patients with idiopathic autoimmune myopathy (21.2 vs. <10%). Serious complications

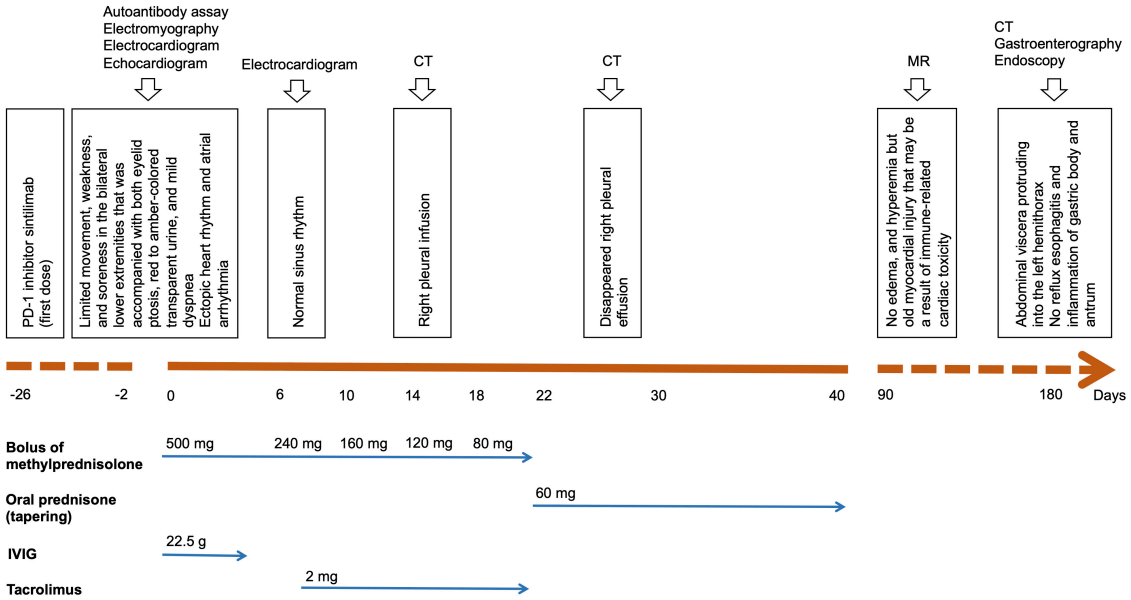

FIGURE 3
Patient timeline chart along with key dates or durations for clinical manifestations, investigations, and treatments with steroids and immunosuppressive agents.

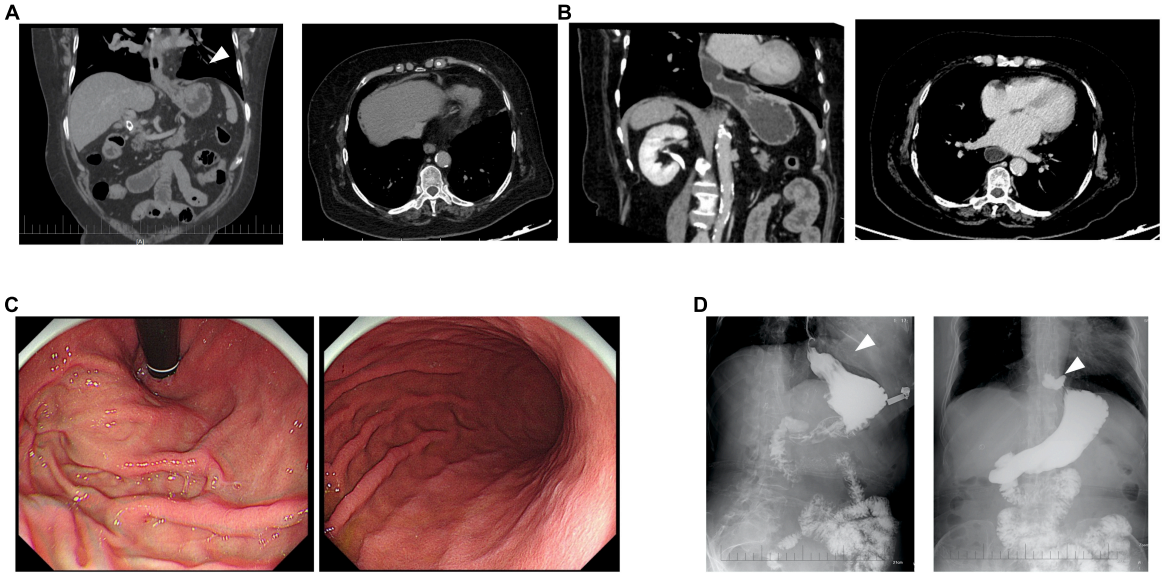

FIGURE 4
Clinical diagnosis of immune checkpoint inhibitor (ICI)-related esophageal hiatal hernia. At the sixth **(A)** and eighth month **(B)** after the onset of immune-related irAEs, a computed tomography (CT) scan for the first time showed abdominal viscera protruding into the left hemithorax (arrow). Upper gastroenterography and endoscopy showed no esophagitis and inflammation of the gastric body and antrum **(C)**, but a clinically confirmed diagnosis of sliding hiatal hernia of the esophagus (type I) was made (arrow) **(D)**.

(defined as long hospital stays, life-threatening events, or residual disability) occurred in 49.4% of patients.

Furthermore, some reported cases presented with simultaneous myocarditis, myositis, and MG secondary to ICI which may represent an overlap syndrome. A report involving 101 cases of ICI-related myocarditis showed that the most commonly occurring concurrent irAEs were myositis (25%) and MG (10%) (5). Patients with ICI-induced myositis frequently complain of oculomotor weakness or eyelid ptosis because of ocular involvement, which can confound the

diagnosis of ICI-induced MG (6). Therefore, the complexity and severity of these overlapping neuromuscular toxicities highlight the urgent need for clinicians to suspect and diagnose multiple simultaneous irAEs and conduct further multidisciplinary approach. Previously reported studies showed that 24.7% (39/158) of cases with ICI-induced myositis and myocarditis developed simultaneous MG. The mortality for patients who had myositis and myocarditis accompanied with or without MG was 32.8 and 25.6%, respectively (**Supplementary Table 1**). As a result, the severity for patients with myositis and myocarditis accompanied without MG is similar to those with MG. After all, myocarditis had the highest fatality rate of 39.7% in 131 reported cases regardless of the co-occurrence of MG (14).

Monitoring the levels of cardiac Troponin T (cTnT) or cardiac Troponin I (cTnI) is helpful to differentiate cardiac from skeletal damage induced by ICIs. Muscle-specific antibody profiling can be used to differentiate baseline autoimmune disease. Based on the clinical presentations and laboratory findings, our patient represents a diagnosis of simultaneous myositis and myocarditis. This patient had increased levels of cTnI, CK, MYO, and elevated liver enzymes as the result of simultaneous cardiac and skeletal muscle damage. ICI-induced myopathy has been described to be associated with $CD8^+$ T lymphocyte and macrophage infiltration (some like granulomas) and necrotizing myositis (4). Matas et al. (15) reported obvious necrosis, macrophages, and muscle regeneration with perivascular inflammatory infiltrates with a large component of macrophagic cells in the pathological review of muscle biopsies of nine patients. Myocarditis induced by ICI has similar characteristics to T cells (especially $CD8^+$ T cells). Unfortunately, pathological analysis of myocarditis or myositis was not available because this patient refused to perform muscle biopsy and endomyocardial biopsy, but a subsequent cardiac MR examination revealed an old myocardial injury that may be a result of immune-related cardiac toxicity.

Diaphragmatic dysfunction as immune-mediated toxicity of ICI therapy is a rarely reported side effect. The presenting symptom of diaphragmatic dysfunction is often dyspnea or orthopnea. At Mayo Clinic, three patients with diaphragmatic dysfunction in the setting of ICI therapy were successfully treated without mortality (16). One patient had a significant, systemic inflammatory response after one cycle of a combination of ipilimumab and nivolumab therapy with a diffuse myopathic process involving the diaphragm and likely the myocardium. It was not an isolated irAE, but rather, was part of a systemic inflammatory process with multiple organ involvement. In the eighth month following the PD-1 inhibitor treatment, the present patient developed a hiatal hernia. Esophageal hiatal hernia refers to the hernia formed by any abdominal tissue structure except the esophagus entering the thoracic cavity through the enlarged esophageal hiatus (17). Age and increased body mass index are characterized as key risk factors for hiatal hernia. The enlargement of the diaphragm-esophageal hiatus is due to the gradual loss of elastin, which makes the ligament around the esophagus and diaphragm relax, resulting in the enlargement of esophageal hiatus and the formation of hiatal hernia. Here, we considered that impaired diaphragm function as a cause of the hiatal hernia was only a clinical diagnosis. First, a hiatal hernia is a relatively frequent clinical disorder, which may occur spontaneously, certainly in a woman with an age of older than 50 years, but this patient had a normal body mass index of 20.2 kg/m^2. Second, she did not have a history of esophageal hiatal hernia and damage of the diaphragm based on her baseline CT scan. Third, ICI-induced myositis can involve multiple striated muscles including cardiac muscle, skeletal muscles, and ocular muscles, as well as the diaphragm, leading to the enlargement of diaphragm-esophageal hiatus and subsequent formation of esophageal hiatal hernia. Recently, Tajima et al. (7) reported a case of fatal fulminant inflammation in the diaphragm resulting from pembrolizumab-related myopathy. Histological analysis showed that massive infiltration of inflammatory cells and muscle fiber necrosis occurred in the diaphragm of the patient, supporting a possible link between ICI-related elated myopathy and diaphragm damage. Thus, the weakness and damage of the diaphragm resulting from immunotherapy-related myopathy or myositis may lead to esophageal hiatal hernia in the present patient. However, here we did not provide substantiation for the causal link with the myositis. Future pathological investigations of the diaphragm are helpful to prove this causal link.

Mild to intermediate irAEs (grade 1 to 2) are clinically well manageable, but more severe cases (grades 3 to 4) are usually life-threatening and require high-dose steroids followed by slow tapering within a few weeks. In cases with severe or steroid-refractory irAEs, most guidelines recommended the administration of immunomodulatory agents such as mycophenolate mofetil, tacrolimus, and tumor necrosis factor-α (TNF-α) inhibitors, as well as anti-thymocyte globulin (18). A multicenter case series by Moreira et al. (19) showed that in 20 cases of myositis (including cases with overlapping MG, polyneuropathy, or myocarditis), 15 patients (79%) were treated with high-dose steroids, and 50% had a complete remission of clinical symptoms (19). In addition to steroids, most patients with myocarditis and MG received IVIG and plasma exchange. In our case study, this patient was initially treated with pulse methylprednisolone and IVIG, and oral tacrolimus was added to steroid therapy when she still suffered from bilateral eyelid ptosis. She received the treatment with steroids and an immunomodulatory agent for a total of 10 weeks. She also restarted systemic chemotherapy in combination with an anti-angiogenic agent due to the significant improvement in clinical presentations. In terms of treatment for esophageal hiatal hernia, different treatment methods should be selected according to patient's condition and classification. This patient with a sliding hiatal hernia had mild symptoms and should be treated conservatively,

and continuing steroids and the immunomodulatory agent is unnecessary. The sliding hiatal hernia seemed to be an anatomical change of the upper gastrointestinal tract and diaphragm as a rare and delayed immune-related neuromuscular manifestation. Laparoscopic surgery should be considered if she experiences gastroesophageal reflux disease symptoms in future. Fortunately, this patient's esophageal hiatal hernia did not progress. She was suggested close monitoring with acid secretion blockade, and her cancer is well controlled.

Conclusion

Here, we reported a case of concurrent myocarditis, myositis, diaphragmatic dysfunction, and esophageal hiatal hernia following treatment with PD-1 inhibitor sintilimab. Autoimmune myocarditis and neuromuscular side effects induced by ICI although rare can be severe and sometimes fatal. The severity for patients with myositis and myocarditis accompanied without MG is similar to those with MG. Early diagnosis and prompt treatment of myocarditis and myositis/MG overlap syndrome can decrease morbidity and possibly mortality because patients often respond well to corticosteroid therapy and other aggressive immunosuppressive agents. Considering the use of PD-1 inhibitors is increasing in cancer patients, physicians should therefore pay more attention to immunotherapy-induced myocarditis with myositis/MG overlap syndrome. Since we hypothesize diaphragmatic hiatal hernia as a potential consequence of immunotherapy-induced myositis, reports on hiatal hernias subsequent to immunotherapy-induced myositis are needed. Future pathological investigations of the diaphragm are helpful to prove this causal link with myositis. Further studies to characterize risk factors and management strategies are also urgently needed.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Shandong First Medical University (No: [2022]-S479). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BY wrote the manuscript and prepared the figures. JX, XW, XL, YG, JC, and KL collected the clinical data. PH performed the radiographical examinations. JW conceived and wrote the manuscript. All authors contributed in their order in writing the manuscript, read, and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.950801/full#supplementary-material

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