General Aspects of Immune-Related Adverse Events

Subjects: Oncology

Contributor: Elia Seguí , Carles Zamora-Martínez , Tanny Daniela Barreto , Joan Padrosa , Margarita Viladot , Javier Marco-Hernández

Immune checkpoint inhibitors (ICI) have revolutionized the landscape of cancer treatment. Although several studies have shown that ICIs have a better safety profile than chemotherapy, some patients develop immune-related adverse events (irAEs), which require specialized and multidisciplinary management.

immune checkpoint blockade | immune-related adverse events | colitis

1. Introduction

The introduction of immune checkpoint inhibitors (ICI), such as anti-PD-1/PD-L1 and anti-CTLA-4, has become a new game changer in the treatment of an ever-growing number of cancer types. Anti-PD-1/PD-L1 antibodies alone in monotherapy or combined with anti-CTLA-4 antibodies or different chemotherapy agents have demonstrated unprecedented clinical efficacy and durable responses in more than 15 cancer types in the advanced setting [1][2]. Moreover, clinical trials with ICIs are further expanding to cancer types historically considered immunological quiescent [3][4] and to earlier settings of the disease [5].

Given their different mechanisms of action compared to cytotoxic chemotherapy and targeted therapies, ICIs' side effects also vary substantially. In fact, due to excessive immunity against healthy organs, the use of these drugs is associated with a wide spectrum of immune-related adverse events (irAEs). Any organ can be hypothetically involved, although some irAEs are much more common than others, such as those affecting the skin, endocrine organs, the gastrointestinal tract, the liver, and lungs. Others, such as neurological disorders and myocarditis, are much less frequent, although they can be very severe, even lethal. The exact pathophysiology underlying irAEs is not well known, but recent studies show that T-cell activation, autoantibody production, and cytokine responses might be involved.

Currently, irAEs are managed according to broadly used but not evidenced-based algorithms. Corticosteroids are used in most moderate and severe cases. For steroid-refractory irAEs, though, there is no standard treatment defined, and description in literature is scarce. Therapetic decisions on these cases are usually made in analogy to autoimmune disorders of the involved organ. Since indications for ICI are rapidly expanding, proper training of clinicians in the early identification and prompt management of irAEs is key for the amelioration of immunotherapy side effects.

2. General Aspects of Immune-Related Adverse Events

2.1. Pathophysiology

The exact pathophysiology underlying immune-related adverse events remains unknown but is believed to be related to the role that both CTLA-4 and PD-1/PD-L1 pathways play in immune homeostasis and the prevention of autoimmune diseases. Research findings indicate that CTLA-4 and PD-1/PD-L1 act in different stages of T-cell activation: while CTLA-4 attenuates T-cell response at a proximal step [6], PD-1/PD-L1 inhibits T-cells at further stages of the immune response and in peripheral tissues [7][8]. Thus, irAEs will differ in patients treated with anti-CTLA-4 from those treated with anti-PD-1/PD-L1, with the effects of anti-CTLA-4 generally being more severe [9].

In most cases, irAEs are thought to be related to autoreactive T cells that bind to shared antigens in both tumor and irAE tissue. In a report of two melanoma patients who died from fatal myocarditis, shared T-cell clones' infiltration was found in both tumor and heart, with no B cells or antibody deposits identified [10].

However, humoral immunity (B cells and autoantibodies) may also play an important role in certain irAEs, with autoantibodies found in patients with thyroid abnormalities, patients who develop type 1 diabetes mellitus, and patients with induced bullous pemphigoid, among others [11][12][13]. Of note, autoantibody frequency is significantly lower than in patients with the same autoimmune disease who did not receive ICI.

In addition, it is also likely that some irAEs might be caused by enhanced complement-mediated inflammation due to the direct binding of ICIs on normal tissue. For instance, it is known that CTLA-4 is strongly expressed in normal pituitary cells, which may explain the higher incidence of hypophysitis seen with anti-CTLA-4 treatments [14].

Finally, some studies suggest that cytokines and chemokines might also be involved in the pathophysiology of irAEs, with elevated levels of IL-17 found in both patients with ipilimumab-induced colitis and preclinical models of colitis [15][16].

2.2. Risk Factors and Predictive Biomarkers

The reason why only certain patients develop irAEs while others do not ever experience them after months of treatment is still not well known. Multiple studies have reported different potential personal risk factors, such as a history of autoimmune disease, high body mass index, and significant kidney disease, among others [17].

Since germline genetic factors are known to be related to some autoimmune diseases, some studies are investigating whether such factors (e.g., HLA genotypes) are also related to the likelihood of experiencing an irAE among patients treated with ICI [18].

In addition, since emerging evidence suggests that the composition of the intestinal microbiota could be associated with immune checkpoint blockade efficacy [19][20], some studies are also investigating whether these variations in the gastrointestinal flora might also influence the risk of developing an irAE [19][20]. In two retrospective studies, a

higher relative abundance of the *Bacteroidetes phylum* was shown to be associated with a reduced rate of ipilimumab-induced colitis [20][21]. Further research is warranted to establish if the manipulation of the intestinal microbiota could reduce the risk of colitis and other irAEs.

Recent studies have also explored the role of circulating blood cell counts in predicting the probability of experiencing an irAE. For instance, in a recent retrospective study of advanced NSCLC patients treated with ICI, a low neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios at baseline were significantly associated with the development of irAEs [22]. Further studies are needed to establish the role of novel predictive biomarkers such as cytokines, microRNAs, and gene expression profiling, among others.

2.3. Incidence and Distribution

More than two-thirds of the reported adverse events related to cancer immunotherapy are due to immune-checkpoint blockade [23]. The incidence of irAEs differs depending on the class of ICI used. A recent large meta-analysis showed an all-grade (Grade 1–5) incidence of irAEs in about 83% of patients receiving CTLA-4 inhibitors, 72% of patients receiving PD-1 inhibitors, and 60% of patients receiving PD-L1 inhibitors [24]. In addition, severe irAEs (Grade 3–5) have been reported in 10–27% of patients receiving anti-CTLA-4 and in 7–20% of patients receiving anti-PD-1/anti-PD-L1 [24][25]. Of note, these frequencies increase significantly when ICIs are administered in combination with another ICI (>90% for all-grade irAEs and around 60% for grade ≥3 irAEs) or with chemotherapy.

Furthermore, the irAEs pattern also varies according to the class of ICI administered (PD-1/PD-L1 inhibitors vs. CTLA-4 inhibitors). When compared to PD-1 and PD-L1 inhibitors, CTLA4 inhibitors are more likely to cause colitis, hypophysitis, and dermatitis, while pneumonitis, hypothyroidism, and skeletal symptoms (myalgias, arthralgias) are less frequent [26].

Lastly, irAEs do not seem to be specific to the type of cancer. However, there is some data denoting that patients with different cancer types receiving the same ICI have different frequencies of specific irAEs, which seems to suggest that the differences seen in the tumor immune microenvironment across different cancer types could also induce different irAEs patterns. For instance, when comparing the development of irAEs after anti-PD-1 treatment in patients with melanoma and renal cell carcinoma, a higher frequency of dermatological, skeletal, and gastrointestinal irAEs was observed in patients with melanoma, but there was a lower frequency of pneumonitis [26].

2.4. Chronological Patterns

Not only the spectrum of potential target organs affected by irAEs is very broad, but also the timing and temporal evolution. irAEs usually commence within 2 to 16 weeks from the start of treatment but can occur at any time, from only a few days after ICI initiation to even years after treatment completion [27]. Noteworthy, combination therapies are not only associated with a greater risk of irAEs, as described previously, but also with an accelerated onset of irAEs, with a median time to onset of around four weeks [25][28]. For both CTLA-4 and PD-1/PD-L1 inhibitors,

dermatologic adverse events are commonly the first to appear, while endocrine irAEs can have a delayed beginning. Pneumonitis and gastrointestinal and liver toxicities, among others, may arise at intermediate points. Even if treatment with ICIs is sometimes given for a long period of time, most studies do not show an increased incidence of irAEs with prolonged treatment. However, later-term toxicity, which will progressively be more relevant since indications are expanding to earlier stages, is still not well known.

2.5. Overall Management Approach to irAEs

Prompt diagnosis and intervention are both crucial to avoid worsening to severe or even life-threatening conditions. However, no prospective trials have defined the best treatment approach for effectively managing irAEs. Thus, the clinical practice remains variable and is mostly based on expert consensus guidelines [25][29][30]. Despite not knowing the exact pathophysiology, irAEs arise from excessive immunity toward normal organs. According to the guidelines, glucocorticoids are usually the first-line immunosuppressive agent used to reduce this excessive state of temporary inflammation, and when glucocorticoids are not initially effective, additional immunosuppressive agents can be used. Handling irAEs will often require a multidisciplinary collaboration among oncologists and other medical specialists, who are increasingly becoming aware of these toxicities.

To summarize, for most grade 1 irAEs, ICIs can be continued, and patients often do not require immunosuppressive treatment. On the other hand, grade 2 irAEs typically require temporary withholding of ICIs and close monitoring to decide if systemic steroids need to be initiated (depending on the severity of the target organ affected or if irAEs persist even after withholding ICI treatment). Patients with grade 3–4 irAEs (severe) frequently need to be hospitalized and receive high-dose steroids.

Prednisone is the most frequently used steroid, and its dosing should be adjusted to the severity of the irAE Once started, steroids should be tapered slowly over 4 to 6 weeks. In severe cases, if no improvement is seen after 48 to 72 h or steroids cannot be tapered without a relapse, additional immunosuppressive agents should be considered.

2.6. Impact of irAEs and Immunosuppression on Immune-Checkpoint Blockade Efficacy

Development of an irAE yields evidence of immune system activation following immune checkpoint blockade. Whether this activation is correlated or not with an improved therapeutic response remains somewhat controversial. Even if it is well known that irAEs are not imperative to obtain a benefit from ICIs, increasing evidence suggests that patients who do experience an irAE have better outcomes in terms of response rate, progression-free survival, and overall survival [31]. However, these data are more robust in patients treated with anti-PD-1/anti-PD-L1 inhibitors than those treated with anti-CTLA-4 inhibitors [31][32]. It is also possible that some irAEs are more related to efficacy than others. For instance, multiple studies of melanoma patients treated with immune checkpoint blockade have shown a correlation between vitiligo and better clinical outcomes [33]. However, these data should be interpreted cautiously since most of these studies do not consider the immortal time bias (ITB), which could be crucial since patients who die or have disease progression are less likely to develop an irAE.

Another important issue, since immune checkpoint blockade functions by increasing immunity, is whether the immunosuppression used to treat irAEs may reduce the efficacy of ICIs. Retrospective studies, mainly with melanoma patients, have not reported a loss of efficacy for patients receiving immunosuppression for irAEs [32][34]. However, prospective studies testing immunosuppressive strategies would be needed to answer this question properly. Of note, even if immunosuppression has not been shown to reduce antitumor efficacy, it does increase the risk for other adverse events (e.g., opportunistic infections) that should be weighed [35].

2.7. Subsequent Treatments after an irAE: Rechallenging the Immune System

Most irAEs resolve eventually after the initiation of immunosuppressive agents. Thus, one of the main concerns in clinical practice is the safety of restarting ICIs after the resolution of irAEs. Prospective data are scarce since no randomized phase 3 trials have evaluated ICI rechallenge after the resolution of severe irAEs.

Retrospective data have shown that subsequent treatment with PD-1/PD-L1 inhibitors after serious ipilimumab-related AEs is safe and associated with only a 3% of recurrent irAEs [36]. Other retrospective studies [37][38] have shown that between 30 and 50% of patients with a previous irAE during treatment with anti-PD-1/anti-PD-L1 had recurrent or new-onset irAEs when resuming treatment; on the contrary, only 18–20% of patients with a previous irAE during combination treatment (anti-CTLA-4 + anti-PD-1), developed a recurrent or new-onset irAE when resuming treatment with only an anti-PD-1. In these studies, patients with myocarditis or severe neurological irAEs were not included.

Therefore, both the ASCO and ESMO guidelines [25][29] recommend permanent discontinuation for all grade 4 irAEs and for most grade 3 myocarditis, pneumonitis, nephritis, hepatitis, and severe neurological toxicities. For all other patients, the decision to resume treatment should be based on the risk–benefit ratio for each patient, considering the severity of the prior irAE, the possibility of alternative treatments, and the overall clinical context of the patient. It is important to bear in mind that even if it is sometimes safe to resume treatment after an irAE, emerging evidence suggests that many patients will continue to derive benefits from immune checkpoint blockade after discontinuation [39].

In some cases, the irreversible organ damage and/or decline in performance status following a severe irAE will also affect and limit the subsequent lines of treatment.

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