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Immune-Related Adverse Events in Cancer Patients Treated With Immune Checkpoint Inhibitors

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Abstract

Purpose of Review—With the advent of cancer immunotherapy and immune checkpoint inhibitors, patients with malignancies can now achieve durable remissions for conditions previously described as terminal. However, immune-related adverse events (irAEs) associated with cancer immunotherapy have become an anticipated consequence of enhanced T cell activation. Through an extensive literature review, we assess the most recent clinical and basic research data concerning immune checkpoint blockade and describe the spectrum of associated irAEs as well as their management.

Recent Findings—Anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies are widely used in the management of an array of tumors with incredible clinical remissions. However, irAEs cause significant morbidity and mortality and in some cases, result in withdrawal of cancer therapy and initiation of immunosuppression.

Summary—While this is an exciting time in oncology, irAEs are a barrier to adequate care and therefore deserve close attention and improved capacity to predict and prevent toxicity. Rheumatologists should be familiar with these topics in the eventuality of patient evaluation and management.

Keywords

Cancer; Checkpoint inhibitors; Adverse events; Autoimmune; irAEs

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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Introduction

The past few years have seen a revolution in cancer treatment. While the concept of cancer immunotherapy is not novel, advances in the field have changed the landscape of cancer treatment. Cancer immunotherapy uses a patient's own immune system to fight cancer by enhanced activation of the acquired immune response. Immunotherapy approaches can be divided into several categories; adoptive cell transfer (ACT), treatment vaccines, oncolytic viruses, and mono- and bi-specific antibodies including immune checkpoint inhibitors [1, 2]. ACT is a cellular therapy, which involves the removal of immune cells as well as tumor infiltrating lymphocytes from patients, followed by in vitro expansion and subsequent return to the patients where they attack the tumor. Alternatively, patients' immune cells can be genetically engineered to express tumor-specific receptors, cultured and returned to the patients, which is known as chimeric antigen receptor T cell (CAR-T) therapy. CAR-T therapy is an approved approach to treat B cell malignancies by removing CD19-positive tumor cells from the body. Other cell types that can be used in this way are natural killer (NK) cells, cytotoxic T cells, and dendritic cells (DC). DC therapy provokes anti-tumor responses by causing DC to present tumor antigens to T cells, which activates them to eliminate transformed cells that present the specific antigens. Treatment vaccines boost the immune system's response to specific antigens expressed on cancer cells and can be used in combination with other anti-cancer approaches for a synergistic effect. Monoclonal antibody technology engineers and generates antibodies against specific tumor antigens, such as those present on tumor cell surfaces in an attempt to detect and eliminate these cells.

Immune checkpoints are regulators of the immune system and are crucial to maintain self-tolerance and to prevent auto-immunity. Some checkpoints, such as CD28, CD40, OX40, and GITR are stimulatory, while others are inhibitory. Inhibitory checkpoints, CTLA-4, LAG3, TIM-3, and PD-1 have been increasingly considered as targets for cancer immunotherapy due to their potential for use in multiple types of tumors [3]. Currently approved immune checkpoint inhibitors (ICIs) block CTLA-4, PD-1, and PD-L1 (a ligand for PD-1). Anti-PD-1 antibodies are designed to bind to PD-1 expressed by tolerant T cells in order to reactivate them and eradicate tumors.

The immunosurveillance paradigm affirms that under homeostatic conditions, the immune system is responsible for clearing malignant cells. It consists of three sequential phases: elimination phase, where malignant cells are removed via the immune system and no overt malignancy is detectable; equilibrium phase, where the quantity of malignant cells and healthy cells are balanced; and escape, where malignant cells overtake healthy tissue and overt cancer is appreciable [4]. Therefore, utilizing the immune system to promote tumor clearance is a logical approach, which has now proven to be an effective cancer treatment. When transformed cells escape immune surveillance and grow into tumor, checkpoint inhibitors are employed to disinhibit the immune system. Not surprisingly, this leads to excessive inflammation, a break in tolerance, and autoimmunity. While this treatment modality has revolutionized cancer treatment, one in every four patients suffers from irAEs, which require immunosuppressive treatment and on occasion, cessation of life saving cancer immunotherapy [5]. This review will discuss checkpoint blockade, indications, irAE pathogenesis, and management.

Regulation of T Cell Activity by Co-receptors

T lymphocytes need engagement of their T cell receptors (TCR) with antigens presented on major histocompatibility complex (MHC) molecules on antigen presenting cells (APC) for activation. This, however, is not sufficient and a second signal is required for complete activation, which can be provided by stimulatory receptors. There are two groups of receptors. The first group is the CD28 superfamily and is composed of CD28 and ICOS, while receptors such as CD27, CD40, CD137 (4-1BB), OX40, and GITR are members of the second group and are part of the TNF receptor superfamily [6]. CD28 is constitutively expressed on approximately 80% of human CD4⁺ T cells and 50% of CD8⁺ T cells [7]. Binding to one of its ligands (CD80 or CD86 on APCs), prompts T cell maturation and expansion. An important class of anti-cancer drugs in development engages stimulatory receptors. Agonistic monoclonal antibodies can activate costimulatory signals to enhance T cell priming. Also, they can be used to reinvigorate exhausted T cells in the treatment of cancer as well as infection. For example, the monoclonal CD28 agonist antibody, TGN1412, was evaluated in clinical trials, but severe inflammatory reactions and other toxicities resulted in discontinuation of the trial [8].

Once the T cell is fully activated, it has great potential to inflict significant damage on invading organisms via the immune response. To keep this system from wreaking havoc, signals from inhibitory receptors are required to bring it back to a state of equilibrium. Many of the inhibitory receptors, such as programmed cell death 1 (PD-1), cytotoxic T lymphocyte-associated protein-4 (CTLA-4), as well as others such as, A2AR, B7-H3, BTLA, KIR, LAG3, TIM-3, and VISTA are under investigation as therapeutic targets [3]. Designed to promote tolerance and to prevent autoimmunity, CTLA-4 and PD-1 are critical for terminating the immune response.

In 1987, CTLA-4 was discovered by scientists from the Goldstein laboratory in Marseille (France) looking for cytotoxic cell surface molecules from the cDNA of CD8 T cells [9]. They found that CTLA-4 had high sequence similarity to CD28 and was also located on chromosome 1 [9]. Initially thought to have a role in activation due to high levels of expression on activated cells, it was not until 1995 that James Allison at UC Berkley found that this receptor acts in an inhibitory fashion and directly opposes the function of CD28 [10]. Supporting this notion, it was reported that CTLA-4 knockout mice develop rapidly fatal autoimmunity. Upon T cell activation, CTLA-4 is the first inhibitory molecule to translocate to the cell surface, where it binds to CD80 or CD86. CTLA-4 counteracts the activity of CD28, and binds the same ligands with greater affinity and avidity than CD28, which leads to cell cycle arrest and inhibition of proliferation [11–13].

PD-1 was identified in 1992, when Ishida et al. attempted to find the gene responsible for programmed cell death via subtractive hybridization [14]. However, this was not supported experimentally, and the inhibitory function of PD-1 was not revealed until PD-1 null mice developed autoimmunity [15]. PD-1 is a type I transmembrane protein, which exists as a monomer on the cell surface. It has two naturally occurring ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2). PD-L1 is found on the surface of many cells, while PD-L2 is restricted to antigen presenting cells (APCs). PD-L2 has a 3-fold

higher affinity for PD-1 than PD-L1. Additionally, high levels of PD-1 are present on T cells chronically exposed to abundant antigen, and dysfunctional or exhausted cells are seen in malignancy and chronic infection. Single-nucleotide polymorphisms (SNP) in the *pdccl1* gene are associated with autoimmunity (e.g., SLE and MS), cancer (e.g., colon cancer) [16, 17], and chronic infection (e.g., hepatitis B). PD-1 is expressed on immune cells (CD4 and CD8 T cells, NK cells, NKT cells, B cells, macrophages, and DC subsets) upon activation of the immune system and chronic inflammation. The cytoplasmic tail of PD-1 has two tyrosine motifs, an immune tyrosine inhibitory motif (ITIM) and an immune tyrosine stimulating motif (ITSM). The tyrosine phosphatase SHP2 is known to bind to the ITSM of PD-1 and propagate inhibitory signaling downstream [18•].

The activation and inhibition of T cells is a dynamic process, where stimulatory and inhibitory receptors work together to fine-tune the T cell immune response. The crossroads where all of these molecules are present simultaneously is at the immunological synapse, the interface between the target and the effector T cells [19]. When signals are being transmitted, the APC displaying peptide loaded on major histocompatibility complex (MHC) binds the T cell receptor. If an inhibitory signal is to be propagated, the APC upregulates PD-L1/PD-L2 or CD80/CD86 and binds inhibitory receptors present on effector cells. These discoveries laid the foundation for using immune checkpoint blocking antibodies in the treatment of cancer.

Immune Checkpoint Blocking Antibodies

One of the mechanisms by which tumors evade immunosurveillance is by upregulating inhibitory immune checkpoint ligands [20]. Tumors can use these checkpoint pathways to inhibit immune cells and to protect themselves by inducing tolerance in the invading T cells. Most of the approved checkpoint therapies block inhibitory receptors (Table 1). Blockade of negative feedback signaling to immune cells thus results in an enhanced immune response against tumors.

The first checkpoint antibody approved by the FDA in 2011 was the anti-CTLA-4 (IgG₁) antibody ipilimumab for the treatment of melanoma. In a seminal phase III clinical trial, it was demonstrated that ipilimumab was superior for overall survival in metastatic melanoma patients, who had been previously treated with other therapies [21]. Serious irAEs were reported at a rate of 10–15% of patients. In addition, several clinical trials with the anti-CTLA-4 (IgG₂) antibody tremelimumab have been completed, but are yet to gain approval and show significance [22–24]. Initial clinical trial results with anti-PD-1 (IgG₄) antibody nivolumab were published in 2010, while its approval was in 2014 [25]. Nivolumab was initially approved to treat melanoma, lung cancer, kidney cancer, bladder cancer, head and neck cancer, and Hodgkin's lymphoma. Subsequently, it was approved for additional indications [26]. Pembrolizumab is another anti-PD-1 (IgG₄) antibody that was approved to treat melanoma and lung cancer [27]. When compared head to head, pembrolizumab showed clear superiority over ipilimumab in the treatment of advanced melanoma [28•]. Also, adverse events were higher in the ipilimumab group (19.9% vs. 13.3%). In 2016, the anti-PD-L1 (IgG₁) antibody atezolizumab was approved for treating bladder cancer [29]. Other anti-PD-L1 antibodies currently in development include avelumab and durvalumab (Table

1). Clinical trials have shown benefits of anti-CTLA-4 therapy also for lung cancer, specifically in combination with other drugs. In ongoing trials, the combination of CTLA-4 blockade with PD-1 or PD-L1 inhibitors is tested on different types of cancer. The combination of anti-PD-1/PD-L1 and anti-CTLA-4 targeting antibodies has been verified in melanoma patients [30]. Treating with concurrent ipilimumab and nivolumab was superior to sequential escalation. However, a higher proportion of patients treated with combination checkpoint blocking antibodies developed serious irAEs. In another study evaluating ipilimumab plus nivolumab or ipilimumab plus placebo, 22% of patients achieved complete response in the combination arm, whereas no complete responses were observed in the placebo group. In patients treated with CTLA-4 blockade, toxicity was observed in up to 60% of patients. Patients receiving anti-PD-1/PD-L1 therapy have more limited toxicity with 24% of patients requiring immunosuppression [31].

Immune checkpoint blockade has improved outcomes for many patients with anti-PD-1 therapy having a better toxicity profile on average, but as with many cancer therapeutics, adverse effects must be managed to allow for greater quality of life and tolerability of treatment.

Immune-Related Adverse Events

The therapeutic success of immune checkpoint blockade comes at a price and many patients develop a wide range of irAEs [5]. Systems that are commonly affected include pulmonary, dermatologic, gastrointestinal, hepatic, and endocrine. Severe and often life-threatening adverse events include pneumonitis and colitis. Overall, drugs targeting the PD-1 pathway cause fewer adverse events than antibodies targeting CTLA-4 [32]. The clinical phenotypes when treated with CTLA-4 versus PD-1 inhibitors are variable. Patients receiving CTLA-4 inhibitors tend to develop colitis and hypophysitis, while those on PD-1 antagonists can have rarer adverse events such as pneumonitis and thyroiditis [33–35].

The mainstay of treatment for irAEs is immunosuppression and interruption of checkpoint inhibitor therapy. Immunosuppressive agents include corticosteroids, mycophenolate mofetil, and tumor necrosis factor- α inhibitors (e.g., infliximab). The management approach is based on experience as no prospective clinical trials have addressed this important question. General and organ specific guidelines have been published by a collaborative effort between the American Society of Clinical Oncologists (ASCO) and the National Comprehensive Cancer Network (NCCN) [36•]. irAEs are graded 1 through 4, with 1 being mild, 2 moderate, 3 severe, and 4 life-threatening [36•]. For grade 1, patients are monitored for worsening of the toxicity. For grade 2, checkpoint inhibition should be withheld and not started until the grade drops to 1, and corticosteroids (e.g., prednisone at 0.5 mg/kg/day) should be initiated if the irAEs do not improve within 1 week. For grades 3 and 4, irAEs treatment should be permanently discontinued, and high-dose corticosteroid therapy (prednisone at 1–2 mg/kg/day) initiated until irAEs drop to grade 1 or lower. Interestingly, a very recent study showed that treatment of ipilimumab induced hypophysitis with high-dose corticosteroids is associated with increased mortality in melanoma patients suggesting that management of irAEs is nuanced beyond typical immunosuppression [37•].

Currently, it is unclear whether anti-TNF therapy should be administered before the development of adverse events particularly in the adjuvant setting.

irAEs are thought to be related to the vigorous activation of the immune system, but the exact pathophysiology is unknown. When tolerance is inhibited, autoimmunity ensues. As described, CTLA-4 terminates early activation of immune responses such as T cell priming in lymphoid tissues, while PD-1 is thought to maintain tolerance later and peripherally in the immune response. The differences between these two checkpoints are demonstrated in mouse models [38, 39]. CTLA-4 knockout mice develop overwhelming rapid fatal lymphoproliferative disease. However, PD-1 knockout mice develop arthritis and lupus like features later in life especially when re-derived in C57/B6 background mice [15]. Similarly, patient irAEs profiles are distinct based on whether they receive anti-CTLA-4 or anti-PD-1 therapy. It is unknown whether T cells or autoantibodies mediate the majority of toxicity in irAEs. In some instances, T cell infiltration is evident based on histology (e.g., myocarditis), but in those cases, the TCR were not sequenced to determine whether or not they were to the same tumor-specific antigen. Vitiligo, also commonly seen in melanoma patients undergoing treatment, suggests cross reactivity between the antigen and T cell clones attacking the melanocytes [40].

Other Considerations

After treatment initiation, irAEs may present at any time, but are most frequently seen weeks to months after checkpoint blockade [5]. Since the T cell autoreactive clones are presumably present long after the cessation of treatment, it is possible that autoimmunity may even present many years after treatment. Early (3 weeks onward) toxicity is most commonly dermatologic for both anti-CTLA-4 and anti-PD-1 treatment [33]. It does not appear that the toxicity correlates with medication dosage suggesting that it is not aggregate.

Based on clinical data, only some patients develop irAEs. It is possible that there is genetic predisposition to irAEs as they are known to be important in other autoimmune and rheumatologic diseases. In autoimmunity, genome-wide association studies (GWAS) have been helpful in identifying genes that may predispose to autoimmunity. Perhaps, GWAS studies in cancer patients can identify patients at risk for irAEs. HLA typing may also be of benefit to identify risk factors [41]. Additionally, the microbiome is a hotbed of discussion, when it comes to predicting treatment response as well as risk of colitis with ipilimumab. Two retrospective studies found that patients with high levels of Bacteroidetes phylum have a decreased risk of colitis [42, 43]. Why or how this is happening is unknown, and further studies are warranted to investigate this topic further.

It is intuitive that patients treated with medications that activate the immune system develop off-target effects. However, whether or not this correlates with disease response to treatment is unclear. Two studies have suggested that irAEs that develop in patients treated with ipilimumab or nivolumab correlate with treatment response [31, 33]. While another study by Topalian et al. did not corroborate these findings in patients receiving nivolumab for advanced melanoma [44]. Whether irAEs determine efficacy of ICIs is yet to be determined,

but it is unlikely that it is related to tumor type as patients with different types of tumors develop similar toxicity depending on antibody target.

It does not appear that use of immune checkpoint blockade simultaneous with immunosuppression affects the effectiveness of cancer treatment. Retrospective analysis of pooled data from 576 nivolumab treated melanoma patients showed that 71% experienced any grade irAEs and 10% experience grade 3 or 4 irAEs [33]. Of all the patients, 24% received systemic immunosuppression with most irAEs resolving, without affecting the progression-free survival [31].

Data is limited and guidelines recommend cessation of ICIs after a serious adverse event, but perhaps switching between targets may be of value. Retrospective data indicates that patients who developed serious irAEs when treated with ipilimumab can safely be restarted on anti-PD-1 therapy [45]. Three percent of these patients developed irAEs suggesting that toxicity is pathway specific as opposed to all-encompassing for checkpoint inhibitors. While there is significant debate about resuming ICI after developing serious adverse events, it is very clear that ICI are absolutely contraindicated, when they result in life-threatening toxicity such as related to pulmonary, nerve, and cardiovascular systems.

As always, when administering medications, there is a risk versus benefit analysis for every patient. However, it is unclear whether patients with pre-existing autoimmunity would deteriorate by receiving immune checkpoint blockade as those patients were originally excluded from clinical trials. Retrospective studies suggest that these patients can be treated with resultant mild or manageable irAEs [45, 46]. Regarding underlying autoimmune disease, it is possible that some patients may experience transient exacerbations of their disease. Overall, it appears the consensus is that these patients should be considered for treatment with ICI if they have high mortality related malignancy and is advised by the treating physician.

Conclusion

We are now in the midst of a renaissance period of innovation for cancer immunotherapy, which has transformed the field of clinical oncology. Sustained durable responses have provided cures to patients previously diagnosed with a terminal illness. However, response is limited to a subset of patients while a large proportion develops irAEs, which can be severe and life-threatening. Individualized treatment strategies may help to curb overexuberant T cell responses and irAEs. More is to be learned about the underlying mechanisms of irAEs, how to predict who will develop toxicity and how to move forward. Importantly, basic science research efforts should be aimed at understanding the process of this de novo model of human autoimmunity to give insight into other autoimmune-mediated conditions.

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Table 1

Monoclonal blocking antibodies

Antibody	Drug	Indication
CTLA-4 IgG ₁	Ipilimumab	Melanoma
PD-1 IgG ₄	Nivolumab	Melanoma, NSCLC, RCC, HCC, Hodgkin's lymphoma, SCC of the head and neck, urothelial carcinoma, gastric ca., solid tumors with high MSI, or MRD
PD-1 IgG ₄	Pembrolizumab	Melanoma, NSCLC, primary mediastinal large B cell lymphoma, Hodgkin's lymphoma, SCC of the head and neck, urothelial carcinoma, gastric ca., solid tumors with high MSI, or MRD
PD-L1 IgG ₁	Atezolizumab	NSCLC, urothelial carcinoma
PD-L1 IgG ₁	Durvalumab	Merkel cell carcinoma, urothelial carcinoma
PD-L1 IgG ₁	Avelumab	Urothelial carcinoma metastatic Merkel cell carcinoma
PD-1 IgG ₄ and CTLA-4 IgG ₁ in combination	Nivolumab and Ipilimumab	Advanced renal cell carcinoma