Treatment of patients with cancer using PD-1/PD-L1 antibodies: Adverse effects and management strategies (Review)

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Abstract. In 2020, there were an estimated 19.3 million new cancer cases and close to 10 million cancer deaths worldwide. Cancer remains one of the leading causes of death. In recent years, with the continuous improvement of our understanding of tumor immunotherapy, immunotherapeutics, such as immune checkpoint inhibitors, have gradually become a hot spot for tumor treatment. Amongst these, programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/PD-L1) related inhibitors, such as nivolumab and pembrolizumab, atezolizumab, avelumab and durvalumab have been shown to exhibit a high level of efficacy in several types of tumors. It has been confirmed that these inhibitors play an important role in the anti-tumor process, significantly improving the survival rate of patients and delaying the progress of the underlying cancer. However, its method of therapeutic interference and potential for damaging the immune system has caused concern regarding its suitability. As these adverse effects are caused by an immune response to endogenous tissues, they are designated as immune-related adverse events (irAEs). In this review, the typical irAEs reported in recent years and the management strategies adopted are highlighted, to serve as a reference in assessing the clinical response to these adverse reactions.

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Contents

1. Introduction

In 2020, there were an estimated 19.3 million new cancer cases worldwide (18.1 million excluding non-melanoma skin cancer) and nearly 10 million cancer deaths (9.9 million excluding non-melanoma skin cancer). It is estimated that by 2040, the global cancer burden will reach 28.4 million cases, an increase of 47% over 2020 (1). There is no doubt that cancer is one of the most important risk factors affecting human health in the world today. Surgery remains the most important and effective treatment approach for the majority of tumor types. However, a large number of tumor patients present with treatment difficulties, such as late diagnosis, inability to tolerate surgery, or a

cancer which spreads with ease or has recurred (2). Therefore, more effective treatment methods are required.

In recent years, immunotherapy has gradually entered the arena. Immune targeted drugs, such as programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/PD-L1) have achieved unprecedented results in the field of tumor therapy. Immunotherapy has become a mainstream direction of development of novel tumor therapeutics and the development of immunotherapeutic drugs has also exhibited explosive growth (3-5). The 2019 anti-cancer progress report released by the American Association for Cancer Research (6) listed cancer immunotherapy with surgery, chemotherapy, radiotherapy and targeted therapies as the five pillars of cancer treatment. Compared with 2017, the total number of global immunotherapeutics in 2019 expanded from 2,030 to 3,876, an increase of 91%, the discovery of potential immunotherapeutic targets has increased by 78% and the number of R&D companies focused on immunotherapy have increased by 60% (7). At present, clinical tumor immunotherapy is primarily divided into four categories: Regulatory T lymphocyte immune checkpoints, chimeric antigen receptor T cell immunotherapy, *in vitro* activation methods and tumor-specific antigen therapy. Among these, the use of antibodies to block cytotoxic T lymphocyte-related antigen 4, PD-1 and its ligand PD-L1 pathways belong to T lymphocyte cellular immune checkpoints (8). The present review primarily focuses on PD1/PD-L1 immune checkpoint inhibitors.

The PD-1 protein is primarily expressed in activated T/B cells, monocytes, dendritic cells, regulatory T cells and natural killer T cells (9), while the PD-L1 protein is widely expressed in antigen presenting cells, activated T/B cells, macrophages and some non-immune cells, such as placental trophoblasts, myocardial endothelium cells and thymic cortical epithelial cells (10). The expression of PD-L1 protein is detectable in several human tumor tissues (11). In a healthy individual, PD-1 binds to the PD-L1 receptor on the surface of T cells, thereby inhibiting the proliferation and activation of T cells, blocking their immune functions and preventing the body from autoimmune diseases (12). However, the tumor tissue also cunningly evades the immune system's attack through the characteristic action of PD-1/PD-L1 (13). Due to the lack of an effective immune response in tumor patients, tumor cells proliferate in large quantities and the PD-L1 receptor protein on the surface can bind to the PD-1 protein on the surface of T cells, leading to the recruitment of tyrosine phosphatase-2 in the src homologous region and then lead to phosphorylation of downstream protein spleen tyrosine kinase and phosphoinositide-3 kinase, inhibit downstream signal transduction, T cell proliferation, cytokine secretion and cytotoxicity (14). Ultimately, this leads to substantial depletion of T cells. PD-1/PD-L1 monoclonal antibody (mAb)-based therapeutics can block the binding between the receptor and its ligand, reactivate T cells and re-initiate the killing of tumorigenic cells (14). At present, there are >10 approved PD-1/PD-L1 mAbs worldwide. In addition, dozens of drugs have been or are about to enter the clinical trial stage. The exploration of their regulatory mechanisms are still the key for improving the development of novel targets, such as FBXO38, a key enzyme for PD-1 ubiquitination and degradation and CMTM6, a key molecule for PD-L1 expression regulation (15-17). In addition, small molecule peptides, treatment-related biomarkers and treatment of drug resistance remain the focus of research (18,19). The mechanism of PD-1/PD-L1 based therapeutics is briefly described in Fig. 1.

According to a study in 2020, the PD-L1 mAb atezizumab combined with bevacizumab in the treatment of advanced liver cancer was significantly improved on traditional sorafenib treatment in terms of overall survival and progression-free survival (20). A clinical study in 2018 reported that the preoperative use of neoadjuvant PD-1 related immunotherapy achieved favorable surgical results in patients with lung cancer (21). The combination of immunization and targeted neoadjuvant therapy-PD-1 mAb combined with TKI also achieved curative effects in liver cancer in preliminary studies (22-24). However, as with almost all therapeutics, PD-1/PD-L1 immunotherapy may inevitably cause patients to exhibit varying degrees of immune-related damage. A phase II clinical trial calculated that the probability of treatment-related adverse events in the treatment of advanced hepatocellular carcinoma with carrelizumab combined with apatinib was 77%; 29% of patients experienced more serious adverse effects including liver damage and two patients died due to treatment (25). According to the statistics of reported adverse reactions, skin injuries including pruritus, psoriasis and nodular dermatitis accounted for 46-62% of adverse events, autoimmune colitis accounted for 22-48% of adverse events and autoimmune hepatitis accounted for 7-33% of adverse events. Endocrine diseases such as thyroiditis, hypophysitis, adrenalitis and diabetes accounted for 12-34% of adverse events. In addition, there are other rare adverse effects including pneumonia (3-8%), nephritis (1-7%), cardiac adverse effects including myocarditis (5%) and nervous system adverse effects (1-5%) (26,27). As these adverse effects result from the immune response to endogenous tissues, they are defined as immune-related adverse events (irAEs) (28).

The present review appraises the typical adverse reactions caused by the use of PD-1/PD-L1 related inhibitors and the management strategies developed in recent years, with the aim of providing an up-to-date reference for clinical response to these adverse reactions in the future.

2. Neuromuscular system

The manifestations of neuromuscular system-related adverse events primarily include symptoms such as tremor, visual disturbances, dysarthria, ataxia, paresthesia and seizures; however, symptoms may also be unspecific, such as headaches, dizziness, fatigue and drowsiness. The most common neuromuscular system-related side effect is myasthenia gravis (29). In addition to cancer, immune checkpoint inhibitors are often used to treat neurological diseases, such as ipilimumab for aseptic meningitis (30,31), Guillain-Barre syndrome (32), transversal Myelitis (33) and enteric neuropathy (34), it is therefore of interest to discuss the nervous system-related side effects of these drugs. A case in China reported a patient with melanoma who developed exertional dyspnea and diplopia after 20 days of nivolumab treatment. Laboratory tests revealed myositis with myocarditis and rhabdomyolysis. Following diagnosis, patients should be administered a course of intravenous immunoglobulin (IVIG). During IVIG, weekly subcutaneous methotrexate and methylprednisolone were administered and discontinued slowly. This coping strategy was clearly

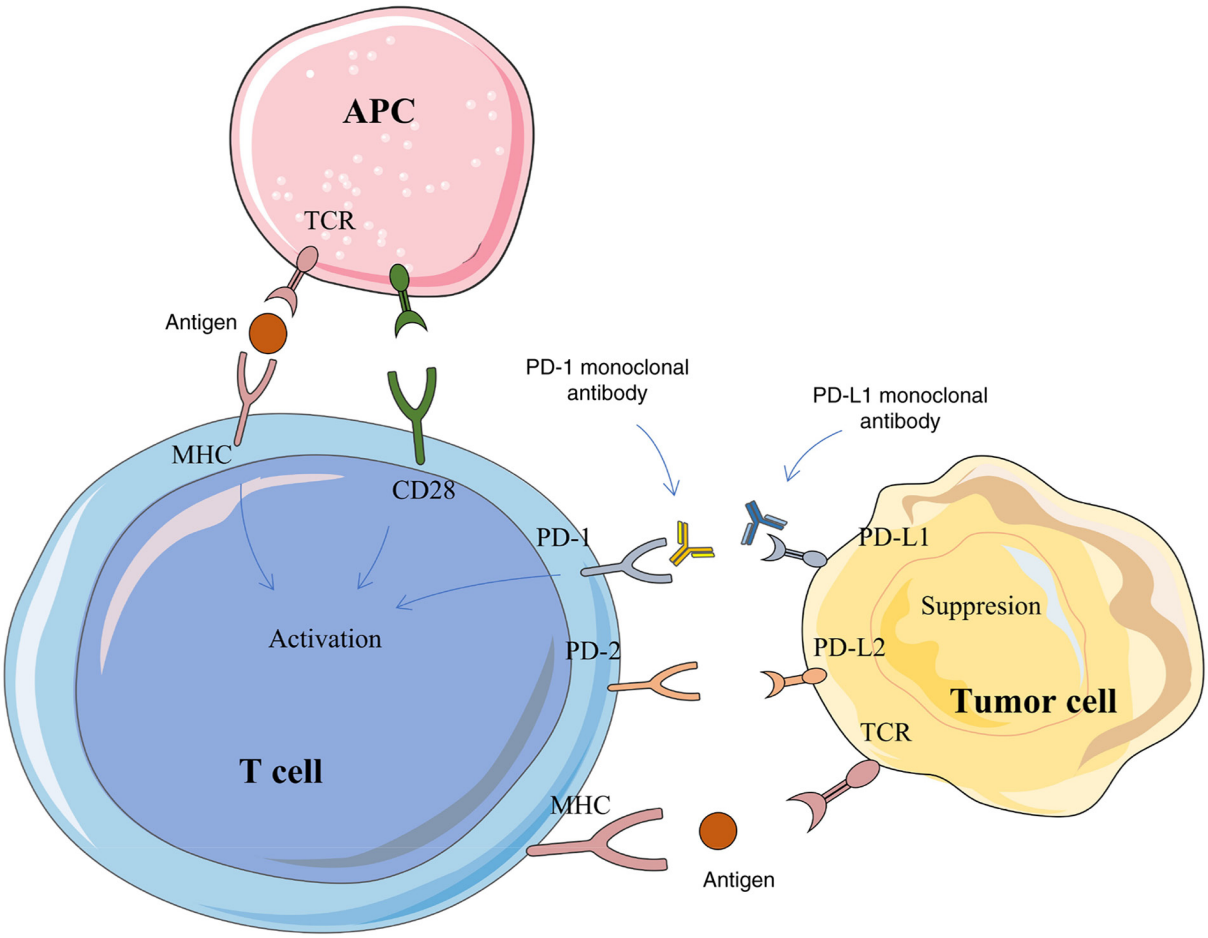

Figure 1. The mechanism of PD-1/PD-L1 in tumorigenesis and development. PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; APC, antigen-presenting cell; TCR, T-cell receptor; MHC, major histocompatibility complex CD, cluster of differentiation.

beneficial to the patient, who gradually exhibited clinical improvements (35). A case report described an 85-year-old woman with metastatic melanoma who developed diplopia after a second cycle of pembrolizumab monotherapy, followed by asymmetric bilateral ptosis; Myasthenia gravis was highly suspected clinically. After a diagnosis was made, the primary treatment options were intravenous immunoglobulin, prednisone and pyridamide. This protocol elicited a rapid clinical response and completely resolved the problems of bilateral ptosis and diplopia. Subsequent treatment included monthly IVIG and daily oral pyridostigmine without any further recurrence of symptoms (36). In addition to the aforementioned reports, there are also reports documenting the adverse effects of myasthenia gravis after the use of pembrolizumab in undifferentiated cholangiopancreatic carcinoma (37-40). The management strategy is administration of pyridostigmine and cessation of pembrolizumab (41). Another article reported on a patient with melanoma who received dacarbazine and ipilimumab. On the fifth treatment cycle, he developed progressive ataxia and dizziness, with intermittent numbness in his left arm. On the seventh cycle, his left arm began to twitch. The final diagnosis was persistent seizures. He was treated with oxcarbazepine plus oxcarbazepine and levetiracetam. After being discharged from the hospital, his seizures continued for three weeks. The management strategy was addition of phenobarbital to oxcarbazepine and levetiracetam. The motor seizures gradually improved after treatment (42). Additional neuromuscular related adverse events and their management strategies are described in Table SI.

3. Respiratory system

Respiratory adverse events are relatively common irAEs. Several life-threatening respiratory events have been reported following the use of anti-CTLA-4 blockers, including tissue inflammatory pneumonitis, sarcoidosis and pulmonary granulomatosis (43-46). The incidence of respiratory-related adverse events in patients receiving anti-PD-1/PD-L1 therapy cannot be ignored. In total, 18-38% of patients most frequently develop a cough and dyspnea. In this subset of patients, 2-9% had a severe grade 3-4 cough and 1-2% had life-threatening grade 3-4 dyspnea (47-49). Below, some of the more serious clinical adverse effects and their management strategies are described.

There is a case report of a patient with poorly differentiated squamous cell lung cancer who was diagnosed with grade 3 immune checkpoint inhibitor-associated pneumonitis (Pneumonia Severity Index classification) after receiving second-line single-agent nivolumab (50). After diagnosis, the management strategy was high-dose glucocorticoid pulse therapy, following which the patient's clinical symptoms gradually eased. Subsequent treatment included oral pirfenidone

for 11 months. During pirfenidone treatment, the CT images and clinical symptoms of the patients showed significant improvements (50). Donato and Krol (51) report a case of allergic bronchopulmonary aspergillosis after four months of treatment with the PD-1 inhibitor pembrolizumab. The final diagnosis was pembrolizumab-induced allergic bronchopulmonary aspergillosis. The management strategy for the patient was administration of corticosteroids and voriconazole. The patient responded to treatment, showing improvement and was able to resume pembrolizumab with a good clinical response. Fragkou *et al* (52) report a lower respiratory tract infection affecting all lobes of a patient with metastatic melanoma following second-line pembrolizumab immunotherapy. Following confirmation of the diagnosis, the management strategy for this side effect was administration of the corticosteroid prednisolone (50 mg/day intravenously). The patient was sensitive to this treatment and his clinical symptoms and radiological results improved rapidly. Unfortunately, three months later, the patient died of advanced metastatic disease in the brain. Additional respiratory related adverse events and their management strategies are described in Table SI.

4. Circulatory system

To date, there have been numerous reports of circulatory system-related adverse events in patients with cancer receiving anti-PD-1/PD-L1 treatment. A case of third-degree atrioventricular block was reported in a patient with metastatic non-small cell lung cancer receiving ipilimumab-nivolumab combination therapy. The patient first developed symptoms of lower extremity swelling after 15 days of ipilimumab and nivolumab treatment and was subsequently diagnosed with left bundle branch block, progressive PR interval prolongation, neutropenia and normocytic anemia. Due to metastatic disease and comorbidities, the patient and medical team chose not to undergo emergency pacemaker placement and the patient was instead scheduled for outpatient event monitoring. Unfortunately, during the hospital stay, the patient was found to have suffered cardiac arrest and eventually succumbed (53). Läubli *et al* (54) report a case of a melanoma patient who developed myocarditis following pembrolizumab treatment. Echocardiography of the patient revealed severely impaired left ventricular function with dyssynchrony and histological analysis of myocardial biopsy showed lymphocytic infiltration, predominance of $CD8^+$ cells and a decrease in $FOXP3^+$ regulatory T cells. The management strategy employed resulted in rapid improvement of symptoms and recovery of left ventricular function and included initiation of corticosteroids and heart failure treatment according to relevant guidelines. Bukamur *et al* (55) document the case of a patient on statins with a history of hypertension and hyperlipidemia who developed muscle mass pain after completing two cycles of nivolumab (240 mg every two weeks). The management strategy for her condition after admission was cessation of statin use and administration of high-dose pulsed steroids. Sinus bradycardia developed and progressed to complete atrioventricular block. After consultation with an electrophysiologist, the patient was implanted with a temporary transvenous pacemaker and then a permanent pacemaker. The overall condition of the patient with this management strategy improved.

5. Digestive system

The probability of digestive system-related AEs in patients with cancer treated with immune checkpoint inhibitors varies with the specific medications administered. The incidence of gastrointestinal reactions in patients treated with anti-CTLA-4/anti-PD-1 combination therapy is 44%, 23-33% in patients treated with CTLA-4 alone and <20% in patients treated with anti-PD-1/PD-L1 alone (56). Gastrointestinal-related irAEs in patients treated with anti-PD-1/PD-L1 primarily include diarrhea, abdominal pain and occasionally fever and some of these will be severe enough to cause substantial damage to the gastrointestinal system (57). Immune-related liver injury is a relatively common irAE. Immune-related hepatitis is the most common liver-related adverse event, affecting ~5% of patients receiving anti-PD-1 therapy, 5-15% of patients receiving ipilimumab monotherapy and one-third of patients receiving combination therapy (57). The following are a few typical digestive system-related adverse events and the associated clinical response strategies adopted. A case report by Tso *et al* (58) documents a patient with metastatic non-small cell lung cancer who presented with acute abdominal pain following long-term treatment with nivolumab and a CT scan showed small dilatation of the proximal ileum, thickening of the vessel wall and perforation near the transition point. The management strategy was a laparotomy and the patient eventually recovered. There is also a report of hepatitis in a woman treated for recurrent renal cell carcinoma. The physicians eventually attributed the hepatitis to the use of nivolumab. The management strategy for this side effect was administration of steroids and the patient began to exhibit improvements in liver function. However, she later developed substantial upper gastrointestinal bleeding secondary to a gastroduodenal ulcer and then developed acute tubular necrosis, ultimately succumbing to the complications (59). Lankes *et al* (60) reported severe diarrhea with ≤18 watery bowel movements per day in a patient with metastatic melanoma treated with ipilimumab. The management strategy was immunosuppression (high-dose steroids and infliximab) combined with parenteral therapy. After nutritional therapy, his condition initially improved, but subsequently worsened. The patient's symptoms improved by changing the treatment strategy to antiviral drugs whilst reducing the application of glucocorticoids. In addition to the aforementioned more common and severe digestive system-related adverse events, additional digestive related adverse events and their management strategies are described in Table SI.

6. Endocrine system

Endocrine-related AEs caused by the use of immune checkpoint inhibitors are more common when treated with anti-CTLA-4 antibodies, whereas a relatively lower incidence of events is recorded in patients treated with anti-PD-1/PD-L1 treatment. Major AEs include hypophysitis, abnormal thyroid function and other less common endocrine diseases such as diabetes and hypercalcemia. In total, ~1% of patients treated with anti-PD-1/PD-L1 develop hypophysitis and 4% of patients develop abnormal thyroid function. Most of these adverse effects are irreversible and require lifelong hormone

replacement therapy (56). The next is a case of a more typical anti-PD-1/PD-L1 treatment-related immune adverse event and the clinical management strategy employed. A 77-year-old woman with stage IV left sigmoid colon cancer developed somnolence and fatigue after receiving second-line pembrolizumab monotherapy and progressively developed polydipsia, nausea and vomiting every day, with progressively more severe symptoms. Diabetic ketoacidosis was diagnosed based on laboratory tests and the management strategy for the patient included fluid replacement, insulin therapy, dose adjustment and electrolyte management. Eventually, the patient recovered and was discharged home for basal and dietary insulin therapy (61).

7. Skin lesions

Immunotherapy-related skin damage is the most common irAE and is very common in patients with cancer treated with anti-CTLA-4 and anti-PD-1/PD-L1. In total, ~50% of patients treated with anti-CTLA-4 exhibit some form of skin damage. The incidence of patients treated with anti-PD-1/PD-L1 who exhibit skin damage is slightly lower at <40% (62). The most common skin-related irAE is skin rashes; most patients report itchy skin. Skin biopsies show large quantities of infiltrated T cells (63,64). The primary treatment measures include topical steroids. Next, a few examples of typical clinical cases reported in recent years are described. Mullangi *et al* (65) reported a patient with renal cell carcinoma who developed psoriasis with nivolumab and showed involvement of the palms and soles. After a diagnosis of palmoplantar psoriasis, he was started on a regimen of topical steroids with triamcinolone acetonide. This did not help his symptoms. Thus, he was instead administered apremilast and retinoic acid and continued nivolumab. After three months, he developed severe diarrhea requiring systemic steroids and infliximab, which improved his condition. No recurrence of symptoms in the last two years of follow-up after discontinuing nivolumab were reported. Acar *et al* (66) also reported localized plaques and hard plaques, but no systemic involvement in a melanoma patient treated with nivolumab. The patient was treated with topical corticosteroids and calcipotriol. Following treatment, the patient's lesions responded well and the patient's condition was ultimately relieved. Mobini *et al* (67) report a patient with renal cell carcinoma who received nivolumab and ipilimumab after developing lung metastases. A total of one month following the first round of treatment, the patient developed large, nontender, firm subcutaneous nodules and plaques on the left forearm and elbow. These nodules and plaques were visible to the naked eye. Skin biopsy showed granulomatous inflammation of the dermis and subcutaneous tissue. Dermatitis nodosa and panniculitis are thought to be secondary to combination therapy with nivolumab and ipilimumab (67). Following consultation with the oncologist, the attending physician decided to discontinue checkpoint inhibitor therapy after the third round. Over the next three weeks of follow-up, the patient reported that the size and stiffness of the lesions were decreasing. There is also a case report of a melanoma patient with a history of psoriasis that worsened during treatment with nivolumab (anti-PD-1). The patient was treated with topical steroids with good results (68). More skin lesion-related irAEs are described in the Table SI.

8. Urinary system

Urinary system-related irAEs rarely occur. In total, ~2% of patients using anti-CTLA-4 will develop urinary system-related irAEs, such as renal injury nephritis and only sporadic adverse effects have been reported in patients treated with anti-PD-1/PD-L1 (69). One of the most serious reports describes a patient treated with anti-PD-1 who exhibited immune rejection following kidney transplantation (70). Next, some of the more common urinary system-related irAEs after the use of anti-PD-1/PD-L1 are described. Schneider *et al* (71) report a patient with melanoma who developed aseptic cystitis during combination therapy with nivolumab and ipilimumab, with diarrhea, frequent urination, severe bladder pain and urgency. The final diagnosis was aseptic cystitis. Treatment with oral steroids was the most effective treatment option. Thummalapalli *et al* (72) report on a patient with BRAF-mutant melanoma who received anti-PD-1 therapy while taking a RAF/MEK inhibitor and experienced severe acute kidney injury at the start of therapy. This process was quickly reversed after symptomatic treatment with corticosteroids. Uchida *et al* (73) report on a patient with lung adenocarcinoma who gradually developed complications of acute tubulointerstitial nephritis following nivolumab treatment. Kidney biopsy showed massive proliferation of $CD38^+$ and IgG^+ plasma cells and massive infiltration of $FoxP3^+$ regulatory T cells. Following the onset of symptoms, the management strategy was discontinuation of nivolumab and initiation of oral prednisolone, which was tapered off gradually. The patient eventually recovered from nivolumab-induced tubulointerstitial nephritis without any treatment for lung cancer. More urinary system-related irAEs are described in the Table SI.

9. Hematological system

Compared with conventional tumor chemotherapy methods that often cause adverse effects of the blood system, tumor patients treated with immune checkpoint inhibitors rarely exhibit related adverse effects, especially for patients treated with anti-PD-1/PD-L1 based therapy. Of those reported, adverse effects primarily included aplastic anemia (bone marrow) and autoimmune hemolytic anemia, which often occurred in the twelfth week of treatment (74-76). Jotatsu *et al* (77) report on a patient with non-small cell lung cancer who developed nivolumab-induced immune thrombocytopenia after nivolumab treatment. The day after the first nivolumab infusion, the patient presented with fever and elevated C-reactive protein levels. Computed tomography of the chest showed no interstitial lung disease or pneumonia. The fever subsided on day 9 and has not recurred since. On day 15 after the first infusion of nivolumab, severe thrombocytopenia developed suddenly and was diagnosed as nivolumab-induced immune thrombocytopenia. This was managed with 60 mg prednisolone per day, which restored the patient's platelet counts and platelet-associated IgG levels, with the patient eventually achieving remission. Another lung cancer patient developed immune-mediated thrombocytopenia and hypothyroidism after receiving nivolumab treatment. The specific manifestation was detection of IgG in the red blood cells of the patient, consistent with the warm autoimmune hemolytic anemia.

The patient recovered after receiving steroid treatment (77). Additional hematological AEs and their management strategies are described in Table SI.

10. Ocular complications

The eyes are not typically regulated by the immune-system and the probability of irAEs there is very low, ~1%. A few sporadic cases report vision-related adverse reactions in patients with cancer receiving anti-PD-1/PD-L1 therapy (62,78). Next, several typical adverse effects of tumor patients treated with anti-PD-1/PD-L1 are described. Obata *et al* (79) report bilateral vision loss in a 63-year-old woman with metastatic cutaneous malignant melanoma 10 days after the second nivolumab injection. Following the onset of symptoms, the patient was started on topical glucocorticoid therapy. This management strategy proved effective and after 3 weeks, the patient's anterior chamber inflammation disappeared. Theillac *et al* (80) report on a man treated with nivolumab for a melanoma of the leg with duodenal and lymph node metastases who suddenly developed bilateral visual impairment and bilateral painlessness after the third infusion of the drug. The patient was eventually treated with oral corticosteroids and his symptoms improved. Additional ocular-related adverse events and their management strategies are described in Table SI.

11. Joint damage

Joint-related irAEs occur in ~15% of tumor patients treated with anti-PD-1/PD-L1 and is considerably higher compared with that in tumor patients treated with anti-CTLA-4 (~1%). These adverse effects often manifest as joint swelling, stiffness, tenderness and erythema, which can last for several years and persist after immunotherapy is discontinued, and joint-related irAEs often occur in patients who have had at least one organ irAE (81-84). There have been case reports of arthralgias in some patients when pembrolizumab or nivolumab have been administered in combination with ipilimumab for treatment of metastatic cutaneous malignancies (85-87). Most patients with this complication receive nonsteroidal anti-inflammatory drugs (NSAIDs), 23.1% require additional low-dose corticosteroids and only 7.6% receive further immunosuppressive therapy. Arthralgia patients recovered following these treatments and exhibited improved PFS and OS (88).

12. Granulomatous venereal disease

There are also some published case reports documenting granulomatous lesions in patients following use of PD-1/PD-L1. Al-Dliw *et al* (89) report on a 65-year-old Caucasian woman with superficial melanoma of the left hip who, 1 year after pembrolizumab treatment, had a biopsy showing chronic granulomatous inflammation in histiocytes. The patient was started on a high-dose of intravenous steroids and showed significant clinical improvement. Noguchi *et al* (90) report on a case of a patient with cT1aN2M1b stage IV left upper lobe pleomorphic carcinoma who received nivolumab as a second treatment and had reduced swelling of the left supraclavicular lymph nodes and left adrenal gland but increased tumor shadowing in the right upper lobe. Bronchoscopy biopsy revealed a granuloma that resembled a sarcomatoid reaction. The patient was not administered a specific targeted therapy and following the withdrawal of nivolumab, the granuloma disappeared. Additional granulomatous-related adverse events and their management strategies are described in Table SI.

13. Other AEs

In addition to the irAEs of the various systems aforementioned, patients using anti-PD-1/PD-L1 have also been recorded to have lymphatic system, oral cavity and other idiopathic irAEs, but the probability of these is very small. In the lymphatic system, a patient with malignant melanoma received pembrolizumab for 3 months. Although there was a partial response to skin metastasis and tumor progression was abated, the patient developed mediastinal lymphadenopathy. The patient underwent selective lymph node resection. The histopathological results were consistent with the nodule response. The patient's pembrolizumab treatment was interrupted and systemic steroid pulse therapy was used, which significantly relieved the lymphadenopathy (91). Lederhandler *et al* (92) report an oral-related irAE in a patient with grade 3 ulcerative oral mucositis in a 78-year-old woman with lung adenocarcinoma 13 months after starting treatment with the PD-1 inhibitor pembrolizumab. The condition was successfully relieved after treatment with prednisone. Additionally, it was reported that patients with metastatic melanoma developed delayed autoimmunity 8 months after stopping the anti-PD-1 antibody nivolumab treatment (93). Therefore, even after the treatment is discontinued, patients receiving immune checkpoint inhibitor therapy need continuous monitoring, especially as the proportion of individuals who have ended treatment after achieving a lasting response increases. Other AEs and the management strategies are listed in Table SI.

14. General management strategies

The irAEs of each system are summarized in the aforementioned sections and Table SI and what is evident is that the treatment strategies for these irAEs vary by patient. However, the common primary management strategies include symptomatic treatment and/or discontinuation of PD-1/PD-L1 mAb. Following the use of PD-1/PD-L1 mAb in patients with cancer who develop nervous system-related irAEs, the earliest symptoms are predominantly a headache, dizziness, fatigue and lethargy. Others present initially with tremors, visual disturbances, dysarthria, ataxia, paresthesia and seizures. Effective coping strategies primarily include intravenous infusion of immune globulin and hormone shock therapy, and it also includes certain targeted symptomatic treatments (32-36,41,42). Respiratory-related irAEs (e.g., post-medication pneumonia, pulmonary aspergillosis and respiratory tract infection) are the earliest manifestations of cough and dyspnea. After these symptoms appear, further laboratory tests can be used confirm the diagnosis (47-49). The primary management strategies for these types of irAEs are drug withdrawal, administration of corticosteroids and targeted anti-inflammatory and antibacterial drugs. For critically ill patients, high-dose hormonal shock therapy should be considered. In the majority of cases, these targeted treatments improve the patient's symptoms (47-52). When a patient develops symptoms such as

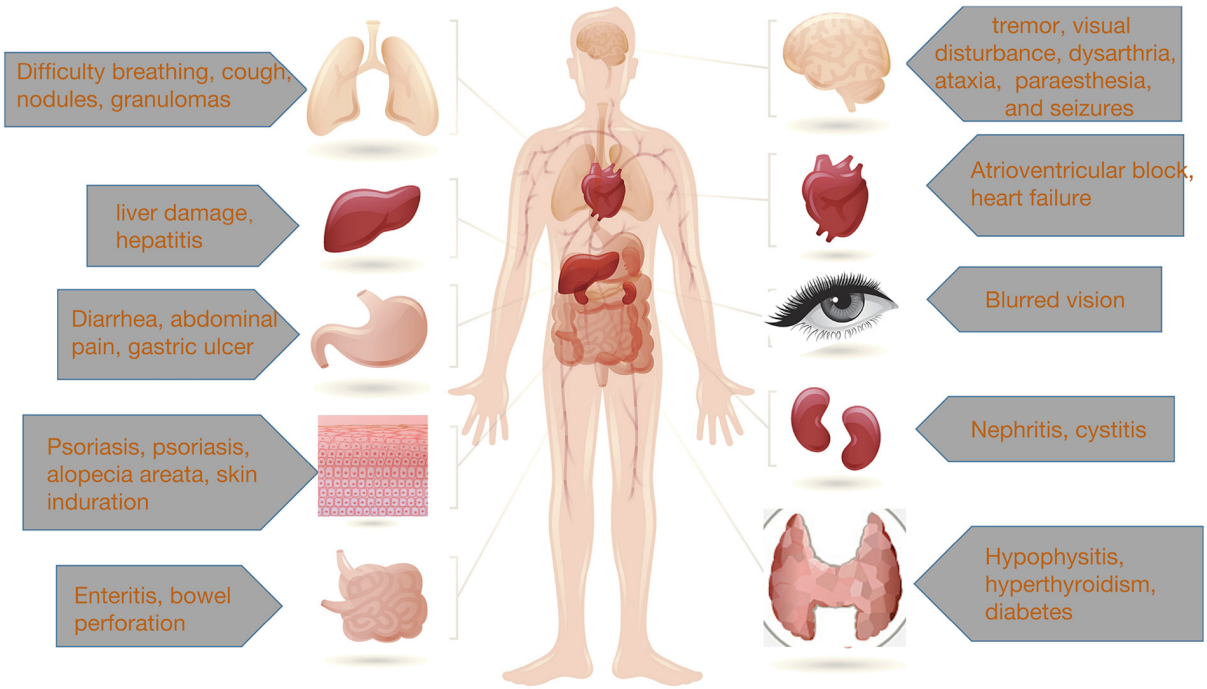

Figure 2. Schematic diagram of irAEs of various systems in the human body after using PD-1/PD-L1 related inhibitors. PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; irAEs, immune-related adverse events.

increased lower limb swelling, muscle pain and precordial pain after using PD-1/PD-L1-related drugs, it is necessary to consider whether it is a circulatory system-related irAEs; thus an electrocardiogram is a necessary test. If irAEs related to the circulatory system (such as atrioventricular block, myocarditis, etc.) are diagnosed, symptomatic treatment should be performed according to the patient's condition, including the application of hormones and pacemaker implantation (53-55). Gastrointestinal-related irAEs in patients treated with anti-PD-1/PD-L1 primarily manifest as diarrhea, abdominal pain and occasionally fever, with a subset of patients exhibiting significant gastrointestinal damage (57). In addition to conventional symptomatic treatment, patients with surgical indications should undergo timely surgical treatment (58-60). Of patients receiving anti-PD-1/PD-L1 therapy, ~1% develop hypophysitis, 4% develop thyroid dysfunction and some patients develop post-medication diabetes (56). Most of these side effects are irreversible and require lifelong hormone replacement therapy (25,61). The most common irAEs in patients receiving anti-PD-1/PD-L1 therapy are skin lesions, which primarily manifest as rashes, skin pruritus, skin plaques and hard plaques, subcutaneous nodules and plaques and psoriasis (63,64). The majority of patients with skin-related irAEs receive topical hormonal therapy with topical corticosteroids and this proves efficacious. However, for patients with severe symptoms, systemic medication should be considered (65-68). Urinary system-related irAEs including nephritis and cystitis are rare. Further laboratory tests should be considered in patients with diarrhea, frequent urination, severe bladder pain and urgency to determine whether urinary-related irAEs have occurred (69,70). Once the diagnosis is confirmed, the management strategies should primarily include oral hormones and symptomatic treatment and whether anti-PD-1/PD-L1 therapy should be discontinued should be evaluated according to the patient's specific situation (71-73). Hematologic-related irAEs have rarely been reported in patients receiving anti-PD-1/PD-L1 therapy. If the patient exhibits changes in blood indicators. such as fever or abnormal C-reactive protein levels during medication, it is necessary to consider whether there are blood system-related irAEs. The primary management strategy is hormone therapy (74-77). Of patients with cancer treated with anti-PD-1/PD-L1, ~15% developed joint-related irAEs, usually characterized by joint swelling, stiffness, tenderness and erythema, which can persist for years after immunotherapy is discontinued (81-84). Most patients receive NSAIDs, 23.1% require additional low-dose corticosteroids and only 7.6% receive further immunosuppressive therapy (88). In summary, targeted therapy for most patients with side effects includes hormone therapy such as corticosteroids and symptomatic therapy, which has proven to be effective in the vast majority of cases.

15. Conclusions

As the number of PD-1/PD-L1-related inhibitors developed increases, an growing number of patients with cancer will benefit from them. However, unfortunately this also means there will be an increase in the number of irAEs and this danger should be taken into consideration when administering these drugs and patients should be carefully monitored throughout the treatment course and even after treatment is discontinued.

A phase II clinical trial calculated a 77% probability of treatment-related adverse events for camrelizumab in combination with apatinib in advanced hepatocellular carcinoma. It was shown that 29% of patients experienced more serious adverse reactions, including liver damage and two patients died as a result of the treatment (25). According to the reported statistics on adverse reactions, skin lesions including

pruritus, psoriasis and nodular dermatitis account for 46-62% of reports, autoimmune colitis accounted for 22-48% of reports, autoimmune hepatitis accounted for 7-33% of reports and endocrine diseases such as thyroiditis, hypophysitis, adrenalitis and diabetes account for 12-34% of reports. In addition, there were other rarer adverse reactions including pneumonia (3-8%), nephritis (1-7%), cardiac adverse reactions including myocarditis (5%) and neurological adverse reactions (1-5%). The types and severity of irAEs differ for patients with different constitutions. In severe cases, it will cause irreversible damage to the patient and potentially even life-threatening complications. As with all treatments, the risks from immunotherapy should be minimized through a careful combination of monitoring, management of side effects and improvements in the therapeutic regimens including the choice of drugs available. Additionally, methods for detecting and diagnosing irAEs at an early stage are of paramount importance.

However, at present, there is no perfect system for detecting and diagnosing these side effects in a timely manner and most physicians just follow a simple 'discovery-symptom treatment' model. This will undoubtedly increase the risk of missed diagnoses and misdiagnoses. Therefore, further exploration of relevant markers and how to deal with these treatment-related immune side effects are increasing becoming an important part of broadening the efficacy of immunotherapy.

The present review summarized the different adverse reactions reported by patients with various types of cancer after treatment with PD-1/PD-L1-related inhibitors and summarized the management options adopted by the attending physician as well as the outcomes of the patients. These adverse reactions include damage to the hematological system, circulatory system, digestive system, urinary system, lymphatic system, neuromuscular system, vision and oral cavity, among others. The purpose of the present review was to highlight the need for improvement of the knowledge of the physicians to these side effects, to improve early detection, early diagnosis and early treatment. In Fig. 2 some of the adverse effects on the various systems listed in this review are summarized for a more intuitive understanding.

In conclusion, immune checkpoint inhibitor therapy has exhibited significant potential. However, such drugs will inevitably cause adverse reactions in clinical applications and the existing case reports and the management strategies used can aid clinicians awareness and guide their response in dealing with these adverse reactions, ultimately improving the health and quality of care for the patients.

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Authors' contributions

GS, XC, HL and GS were responsible for gathering the related research and designing the review. WY, XK and ZZ were responsible for creating the figures. HC, XS, GS and WT contributed to study design, interpretation of the research articles, editing of the manuscript and critical revision of the manuscript. PT and GS contributed to respond to reviewer comments and make revisions. PT contributed to the language editing. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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