REVIEW

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Advances in targeting programmed cell death 1/programmed cell death-ligand 1 therapy for hematological malignancies

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Abstract

Programmed cell death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) are important immune checkpoints, and their interactions can mediate immune suppression in the tumor microenvironment. Targeting PD-1 and PD-L1 are immune checkpoint inhibitors that bind to PD-1 and PD-L1, respectively, to block the signal pathway between the two and increase the immune response. They are widely used in tumor treatment and have good efficacies for malignant melanoma, renal cell carcinoma, and non-small cell lung cancer, among others. In addition, for hematological malignancies, studies targeting PD-1 and PD-L1 have achieved gratifying results. This article briefly reviews the mechanisms of action and clinical and hematological malignancy applications of targeting PD-1 and PD-L1.
Keywords: PD-1, PD-L1, mechanism of action, hematological malignancy

Introduction

In recent years, tumor immunotherapy has gradually become a hot spot in the field of tumor treatment and has shown good prospects in cancer treatment [1], which is also one of the most promising research directions in tumor treatment. Programmed cell death 1 (PD-1; also known as CD279 [2]) is a member of the B7 receptor family. Its ligands are programmed cell death-ligand 1 (PD-L1; also known as CD274) and programmed cell death-ligand 2 (PD-L2; also known as CD273), which are expressed by multiple types of cells [3]. Among them, PD-1 and PD-L1 are the most common immune checkpoints, which mainly inhibit stimulation, negatively regulate T-cell functions, and weaken the immune response to tumors. Therefore, targeting PD-1 and PD-L1 can block the combination of PD-1 and PD-L1 to restore the antitumor effect of the immune system. This article briefly reviews its mechanism of action and application in hematological malignancies.

Mechanism and overview of PD-1/PD-L1

Structural features

PD-1 is a transmembrane protein with 288 amino acids and belongs to the immunoglobulin superfamily. It is present in lymphocytes, natural killer (NK) cells, monocytes, and dendritic cells [4]. PD-1 contains an Ig variable-type extracellular domain, a transmembrane domain, and a cytoplasmic tail [5]. The cytoplasmic tail has an immunoreceptor tyrosine-based inhibitory motif (ITIM) [6] and immunoreceptor tyrosine-based switch motif (ITSM). After PD-1 binds to PD-L1, the ITIM and ITSM of PD-1 are phosphorylated by Src family tyrosine kinases [7], thereby inhibiting T-cell activity and proliferation. Thus, PD-1 has dual roles in immunological tolerance: induction and maintenance of peripheral tolerance [8]. PD-1 can also bind to B7-H1 and the crystallizable fragment (Fc) fusion protein to inhibit the production of interleukin-2 (IL-2) in lipopolysaccharide (LPS-stimulated RAW264.7

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cells by inhibiting the Janus N-terminal kinase signaling pathway [9].

Programmed cell death-ligands (PD-Ls) contain PD-L1 and PD-L2. Whereas PD-L1 is constitutively expressed and upregulated in T cells, B cells, macrophages, dendritic cells, endothelial cells, epithelial cells, and muscle cells, PD-L2 is only expressed on the surface of dendritic cells, macrophages, and bone marrow-derived mast cells [10]. Moreover, they have similar exon organizations of the 5′-untranslated region; a signal sequence; IgV-like, IgC-like, and transmembrane domains; and cytoplasmic exons 1 and 2 with the 3′-untranslated region [11]. PD-L1 has many functions; when it binds to PD-1, it can inhibit T-cell proliferation and cytokine production [11]. PD-L1 can also interact with B7-1. Regarding its mechanism of action, many theories have been proposed, with some studies suggesting that cis-PD-L1/B7-1 on antigen-presenting cells (APCs) disrupts the transbinding of PD-1/PD-L1. Through this mechanism, APCs expressing substantial amounts of B7-1 mediate diminished T-cell inhibition via PD-1 [12], which provides a relevant basis for combination therapy with B7-1 and PD-L1. The role of the combination of PD-L2 and PD-1 in regulating the differentiation and function of T cells remains to be determined because both coinhibitory and costimulatory functions have been reported [13]. Therefore, drug designs are mainly focused on PD-1 and PD-L1 targets. PD-L2 can also interact with repulsive guidance molecule b (RGMb) to regulate respiratory tolerance [13].

Mechanisms

PD-1 can bind to PD-Ls. When binding to a PD-1 ligand on antigen-presenting cells, PD-1 can shut down self-reactive T cells and induce peripheral tolerance. While binding to a PD-1 ligand on parenchymal cells, PD-1 can maintain tolerance and prevent tissue destruction by inhibiting effector T cells [8]. The mechanisms of action of targeting PD-1/PD-L1 are shown in Figure 1.

The PD-1 pathway has various mechanisms of action. After the ITIM and ITSM of PD-1 are combined, they are phosphorylated by Src family tyrosine kinases, and Src homology 2 domain-containing phosphatases (SHPs) are further recruited to the phosphorylated tyrosine residue. SHPs can dephosphorylate downstream signaling pathways, thereby blocking cell cycle progression [14]. SHPs can also inactivate zeta-chain-associated protein kinase 70 and protein kinase C-θ [2]. In addition, Francisco and colleagues demonstrated that PD-L1 can induce and maintain Tregs and enhance immune suppression at the organismal level [15].

Clinical application

Immune checkpoint inhibitors have become a key method of cancer treatment, especially targeting PD-1/PD-L1. In recent decades, an increasing number of related drugs have been used to treat malignant tumors.

Among PD-1 inhibitors, pembrolizumab [16] was first approved by the Food and Drug Administration (FDA) in September 2014 for the treatment of melanoma, non-small cell lung cancer (NSCLC), and so forth. Three months later, nivolumab was approved for release in the market [16] for the treatment of melanomas that are unresponsive to other drugs. In the same year, MPDL3280A was shown to be a breakthrough therapy for metastatic bladder cancer and NSCLC in February of the following year. In China, Opdivo (nivolumab) was first approved for release in the market in June 2018; and Keytruda (pembrolizumab), in July. Thereafter, several drugs have been launched in the market.

Among PD-L1 inhibitors, atezolizumab was first approved by the FDA for the treatment of bladder cancer, followed by durvalumab, avelumab, and so forth. At present, two PD-L1 inhibitors have been approved for release in the market in China, namely Imfinzi (durvalumab) in Decem-

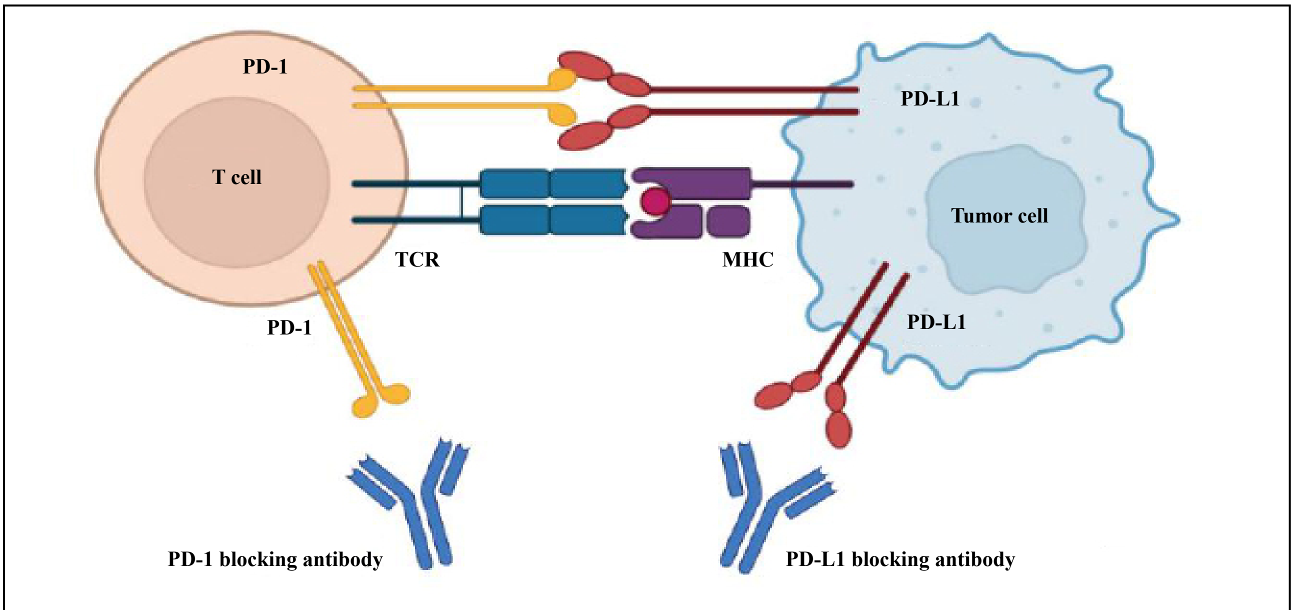

Figure 1. The mechanisms of action of targeting PD-1/PD-L1.

ber 2019 and Bavencio (atezolizumab) in February 2020. However, with the progress of drug research, drug resistance has gradually become an urgent problem to be solved. Research has shown that the tumor-immune cycle is divided into the following seven steps: the release of cancer antigens, cancer antigen presentation, priming and activation, trafficking of T cells to tumors, infiltration of T cells into tumors, recognition of cancer cells by T cells, and killing of cancer cells. Given that PD-1/PD-L1 blockade is primarily involved in step 7, any abnormalities in the previous steps may lead to drug resistance [17], such as lack of tumor antigen expression, dysbiosis of the normal gut microbiome, and migration disorders of T cells. Therefore, for combination drugs, the PD-1/PD-L1 pathway can be used as the cornerstone of the combined checkpoint blockade program to antagonize additional inhibitory signals and thereby improve the immunity efficacy of checkpoint blockade in cancer treatment [18]. At present, the most commonly used combination drugs are as follows: Radiotherapy can cause the release of tumor antigens and increase the immunogenicity of tumors [19]. Vaccines, CD40 agonists, and toll-like-receptor agonists can promote dendritic cell (DC) cross-presentation to enhance the anti-tumor response of T cells. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) blockers, CD137 agonists, and inflammatory cytokines such as IL-2 can enhance the initiation and activation of T cells. Block inhibitory immune checkpoint molecules such as T-cell immunoglobulin and mucin domain 3 (TIM-3) and lymphocyte-activation gene 3 (Lag-3) [17] can reduce the drug resistance of targeting PD-1/PD-L1 and enhance the therapeutic effect.

Application of targeting PD-1/PD-L1 in hematological malignancies

With the progress of drug research, targeting PD-1/PD-L1 has gradually been used in hematological malignancies. Relevant clinical trials have been conducted for drugs such as nivolumab and pembrolizumab, and some drugs have been approved for use in the clinical treatment of certain hematological malignancies. According to research, for hematological malignancies, targeting PD-1/PD-L1 is most effective for lymphoma, followed by leukemia, but least effective for multiple myelomas (MMs). This may be related to the expression levels of PD-L1 in different types of tumors and in the tumor microenvironment.

Several studies have examined the usefulness of PD-L1 expression levels. Immunohistochemistry (IHC) assays have demonstrated that response rate directly correlates with PD-L1 expression level. In addition, patients with high PD-L1 expression levels in tumor-infiltrating immune cells showed better therapeutic responses and clinical outcomes [20]. However, the expression levels of PD-L1 on neoplastic cells and in the tumor microenvironment vary between different subtypes, and the prognostic implications of PD-L1 expression remain unclear [21]. Future studies need to further delineate the mechanisms of PD-L1 expression and explore more possibilities in depth.

In addition, the therapeutic effect of targeting PD-1/PD-L1 may also be related to the tumor microenvironment, in which inflammatory cytokines, especially interferon γ (IFN-γ), are present. Inflammatory cytokines stimulate not only tumor cells that express PD-L1 and PD-L2 but also other types of cells in the tumor microenvironment, such as macrophages, dendritic cells, and stromal cells, that increase the expression level of PD-1 ligand [22].

Therefore, among hematological malignancies, lymphoma has the best therapeutic response. In particular, the copy numbers of the PD-L1 and PD-L2 gene loci in most patients with Hodgkin lymphoma (HL) are amplified, which leads to the upregulation of PD-L1 and PD-L2 expressions. Therefore, targeting PD-1/PD-L1 has a good therapeutic effect on HL. In non-HL (NHL), targeting PD-1/PD-L1 has a good therapeutic effect on diffuse large B-cell lymphoma (DLBCL). Nearly 20% of DLBCLs not otherwise specified (NOS) have PD-L1 overexpression, and the structural abnormality of the 9p24.1 chromosome is significantly related to PD-L1 expression. Targeting PD-1/PD-L1 also has a good therapeutic effect on NK/T-cell lymphoma (NKTCL). The mRNA levels of PD-L1 and PD-L2 in patients with NKTCL are significantly upregulated. However, patients with mantle cell lymphoma (MCL) have weaker PD-L1 and PD-L2 on the surfaces of B and T cells than healthy individuals, and experiments have shown that, targeting PD-1/PD-L1 is ineffective in these patients. Targeting PD-1/PD-L1 has a weaker therapeutic effect on leukemia than lymphoma. Patients with acute myeloid leukemia (AML) have a significant increase in PD-1 expression on T cells due to the imbalance of the PD-1 pathway and the tumor microenvironment. Targeting PD-1/PD-L1 has the weakest therapeutic effect on MMs. Experiments have shown that in patients with MMs, the expression levels of PD-L1 in plasma cells are different and higher than those in healthy volunteers.

Regarding the specific application of targeting PD-1/PD-L1 to hematological malignancies, this article describes its effects.

Lymphoma

(1) Hodgkin lymphoma

For most HLs, cytogenetic studies have shown that the copy numbers of the gene loci of PD-L1 and PD-L2 are amplified, which leads to the upregulation of the surface expressions of PD-L1 and PD-L2 [23]. Therefore, targeting PD-1/PD-L1 has a better therapeutic effect on HLs.

1) Relapsed/refractory HL

Currently, nivolumab and pembrolizumab are approved by the FDA for the treatment of advanced relapsed/refractory (r/r HL). In addition, a previous study found that 70% of patients with r/r HL responded to PD-1 inhibitors, of whom 20% had a complete response [24].

A retrospective study included 53 patients with r/r HL from nine US centers who were treated with nivolumab. The overall efficacy rate obtained by the discoverer was

68%; 12-month progression-free survival rate, 75%; overall survival rate, 89%; complete remission rate, 45%; and partial remission rate, 23% [25], indicating that nivolumab has a good treatment effect on HL. A clinical trial published by the European Hematology Association (Abstract: PF431) studied the use of nivolumab and brentuximab vedotin (BV) as combination therapy for the treatment of 10 patients after failure of nivolumab monotherapy. The median follow-up time was 10.8 months (range, 7.4–13 months). The objective response rate of the treated patients was 70%, the complete response rate was 30%, and nine patients (90%) had treatment-related adverse events (AEs), of which nausea and peripheral neuropathy were the most common. This shows that the therapeutic effect of nivolumab + BV is similar to that of monotherapy. Thus, nivolumab + BV is expected to be an effective rescue plan for patients with r/r HL who have failed to respond to nivolumab monotherapy. In addition, a recent study found that for 59 patients with r/r HL treated with nivolumab and BV after autologous hematopoietic cell transplantation, the 18-month progression-free and overall survival rates were 95% and 98% [26], respectively, indicating that nivolumab is also expected to be used for the consolidation of autologous hematopoietic cell transplantation.

Pembrolizumab therapy is also effective. A multi-cohort phase II study found that pembrolizumab has clinical activity in patients with r/r HL, with an objective response rate of 65–72% and a complete response rate of 22% [27]. A phase I clinical study found that after treatment with pembrolizumab, of 31 patients who failed treatment with an anti-CD30 monoclonal antibody, 90% had tumor shrinkage, with a total efficacy rate of 65% [28], showing a satisfactory result. Pembrolizumab can also be combined with other drugs. A phase II study found that 32 (94%) of 34 patients achieved complete remission after using pembrolizumab-GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) as a second-line treatment for r/r HL [29]. This shows that the treatment is better than the standalone treatment and is an efficient and well-tolerated program.

In addition to the two above-mentioned drugs, many drugs are effective for the treatment of r/r HL. A study used sintilimab to treat 96 patients with r/r cHL and showed that as of September 30, 2019, 57.3% of patients completed the treatment. After 2 years of treatment, the 2-year overall survival rate was 96.3%. The long-term follow-up results showed that in addition to the high response rate, sintilimab also showed long-lasting efficacy and good long-term safety [30]. A clinical study used camrelizumab combined with decitabine to treat 51 patients with r/r cHL who failed treatment with anti-PD-1 therapy. The median progression-free survival time with the combination therapy was significantly longer than that with the previous anti-PD-1 monotherapy. In patients who achieved complete remission at 24 months, 78% observed a durable response [31], indicating that in patients with r/r cHL, the use of camrelizumab and decitabine as third-line therapy or beyond has tolerable and significant antitumor activity.

2) Untreated HL

With the widespread application of targeting PD-1/PD-L1 in r/r HL, an increasing number of clinical trials have investigated its therapeutic effect on newly treated HL. In a recent phase II study, nivolumab and BV combination therapy in patients older than 60 years among the evaluable patients, the best objective response rate was 95%, proving that BV-nivo is effective for elderly patients with untreated HL who have comorbidities [32].

(2) Non-Hodgkin lymphoma

NHL is divided into B-, T-, and NK/T-cell lymphomas. B-cell lymphomas include DLBCL, follicular lymphoma (FL), and MCL. This article elaborates on these.

1) Diffuse large B-cell lymphoma

In DLBCLs, PD-L1 can be expressed by B cells in DLBCL tumors and non-malignant cells (e.g., macrophages) from its immune microenvironment [33]. According to reports, nearly 20% of DLBCL NOS have genetic abnormalities and chromosomal changes, which lead to PD-L1 overexpression [34]. Among these abnormalities, the structural abnormality of the 9p24.1 chromosome is significantly related to the expression of PD-L1 in DLBCL [35].

For the treatment of DLBCL, preliminary trials have shown that PD-1 inhibitors have limited effects on DLBCL. Nivolumab can be used alone, as a phase I study found that the use of nivolumab alone in the treatment of 81 patients with lymphoma and myeloma (11 cases of DLBCL) had an efficacy rate of 36% [36]. Nivolumab can also be used in combination therapies. In the combined use of nivolumab and ipilimumab in the treatment of 65 cases of hematological malignancies (10 cases of DLBCL), only three cases responded [37], indicating a poor treatment effect. Recently, a study (NCT03305445) that included six patients with DLBCL treated with nivolumab and ipilimumab after conventional treatment and before stem cell transplantation showed that three (50%) of the patients benefited from and well tolerated the transplantation, indicating an acceptable effect. A clinical trial evaluated pembrolizumab combined with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the treatment of 30 patients with untreated DLBCL and revealed that the therapy had comparable toxicity with the standard R-CHOP therapy, but two patients developed grade 3 immune-related AEs. The overall and complete response rates were 90% and 77%, respectively, and the 2-year progression-free survival rate was 83% [38], which was better than pembrolizumab monotherapy. Several later studies were conducted to examine the effect of pembrolizumab combined with other drug treatments.

In addition to the two abovementioned drugs, many other drugs have been studied for the treatment of DLBCL. A study of zanubrutinib in combination with tislelizumab in 69 patients with B-cell malignancies (including 27 with DLBCL) showed an objective remission rate of 37% in patients with DLBCL, of whom four (14.8%) had a complete remission and six (22.2%) had a partial remission [39]. In germinal center B-cell-like (GCB) and non-GCB (NGCB) DLBCLs, the objective remission rates were 33.3% and 40%, respectively, indicating a poor therapeutic effect. A clinical trial of atezolizumab combined with R-CHOP in the treatment of 42 patients with untreated DLBCL showed that 31 patients (77.5%) achieved complete remission and four (10%) achieved partial remission according to an independent review committee [40], which indicate a promising effect.

In some special types of DLBCL, targeting PD-1/PD-L1 has a better curative effect. In primary central nervous system lymphoma (PCNSL), owing to the changes in chromosome 9p24.1 [41], the PD-L1 expression level is increased, so targeted therapy drugs have a better effect. A clinical trial that used nivolumab to treat four patients with r/r PCNSL and one patient with relapsed primary testicular lymphoma (PTL) revealed that all five patients had objective responses, including complete remission in four patients and partial remission in one patient [42], indicating that the treatment has high efficacy, had a long-lasting curative effect, and can improve central symptoms at the same time. However, a phase II trial of nivolumab for r/r PCNSL or r/r PTL showed that the objective response rate assessed by blinded independent central review (BICR) was 6.4%, and the progression-free survival period was 1.41 months [43], indicating that the efficacy of targeting PD1/PD-L1 in PCNSL must be confirmed by more prospective clinical studies. An ongoing phase II clinical trial of nivolumab and ibrutinib for r/r PCNSL is currently recruiting patients [44].

Primary mediastinal large B-cell lymphoma (PMBCL) is similar to PCNSL because of the chromosome changes that lead to the overexpression of PD-L1; thus, the application of targeted drugs has a better effect. According to a report, the objective response rate of the first batch of 19 patients in the PMBCL cohort was 41% [45]. The National Comprehensive Cancer Network guidelines recommend pembrolizumab for r/r PMBL. A phase II trial of pembrolizumab in the treatment of 53 patients with r/r PMBL showed an objective response rate of 45% and a complete response rate of 21% [46], indicating effective outcomes. A clinical trial of nivolumab combined with BV in the treatment of 30 patients with r/r PMBL showed that at a median follow-up of 11.1 months, the objective response rate was 73%, the complete response rate assessed by each investigator was 37%, and the remission rate was 70% [47], which is better than the treatment alone.

The overexpression of PD-L1 in Epstein-Barr virus (EBV)-associated lymphoma [48] is thought to be mediated by the latent membrane protein 1 (LMP1) encoded by EBV [49], which makes it sensitive to PD-1 blockade. An experiment was conducted to study the effect of PD-1 blockade on the antitumor immunity of lymphoma cells and revealed that PD-1 blockade exerted a highly effective role in EBV+ DLBCL [50], stronger than that of EBV− DLBCL, indicating that targeting PD-1/PD-L1 will have a better effect on DLBCL. We look forward to conducting more clinical trials to verify the efficacy of the drug in the future.

2) Follicular lymphoma

Unlike DLBCL, most FL tumor cells do not express PD-L1 or PD-L2 [33], but the immune infiltrates expressed PD-L1 and PD-L2 at normal levels and overexpressed PD-1 [33]. Cells expressing PD-1 include not only cells derived from tumor-infiltrating lymphocytes (TILs) but also follicular helper T cells from lymphoma follicles or residual germinal centers [51]. In addition, PD-1+ TILs in FL and DLBCL positively correlate with prognosis, and the presence of PD-1+ TILs in lymphoid tumors may indicate the source of the cells [52].

Regarding the treatment of FL, a phase I study of nivolumab for the treatment of r/r hematological malignancies (including 10 patients with recurrent FL) showed an objective remission rate of 40% [36]. A phase II clinical trial found that the use of nivolumab as the first-line treatment for immune initiation, followed by treatment with nivolumab and rituximab, in 39 patients with FL at a median follow-up time of 17.5 months achieved an overall response rate of 92%, a remission rate of 54%, and a median remission time of 5 months. In 25 evaluable patients, the 12-month progression-free and overall survival rates were 72% and 96% [53], respectively, indicating that the effect of the regimen is better than that of nivolumab alone. A phase II clinical trial demonstrated that pidilizumab combined with rituximab in the treatment of 30 patients with relapsed FL had a total efficacy rate of 66%, with 52% of the patients achieving complete remission and 14% achieving partial remission [54], indicating a good overall effect.

3) Mantle cell lymphoma

On the basis of experiment results, PD-L1 and PD-L2 expressions on the surface of B and T cells in patients with MCL are weaker than those in healthy individuals [55]. Therefore, these results show that targeting PD-1/PD-L1 is not effective for the treatment of MCL and should not be used as a related drug target.

4) T-cell lymphoma

Studies have shown that TCL overexpresses PD-1 [56] according to the severity of the disease, so targeting PD-1/PD-L1 has a certain therapeutic effect on TCL. Targeting PD-1/PD-L1 is mostly used for r/r peripheral T-cell lymphoma (PTCL). A phase I clinical study used nivolumab to treat 23 patients with r/r TCL (of whom five had PTCL) and showed that the partial response rate of the patients with PTCL was 40% [36]. A clinical trial (NCT03075553) used nivolumab in the treatment of 12 patients with r/r PTCL and showed that the response rate of participants who achieved complete or partial remission was 33.3%, proving that nivolumab is effective for the treatment of PTCL. Pembrolizumab combined with romidepsin has been approved by the FDA for the treatment of r/r PTCL. It has been applied in the treatment of r/r PTCL in a phase

I/II clinical study (NCT03278782) with 15 evaluable patients, with an objective response rate of 44% and a complete remission rate of 20%.

Regarding untreated T-cell lymphoma, a previous study showed a significant increase in PD-1 expression in peripheral CD4+ and CD8+ T cells. After treatment, the decline in PD-1 expression level was similar to that in healthy people, so we can infer that targeting PD-1/PD-L1 also has a good effect on T-cell lymphoma. Few clinical trials have been conducted on the treatment of untreated T-cell lymphoma, and targeting PD-1/PD-L1 is expected to have more applications in the future.

5) NK/T cell lymphoma

The mRNA expression levels of PD-L1 and PD-L2 in extranodal NKTCL (ENKTCL) were significantly upregulated, and studies have found that PD-L1 protein is expressed in tumor cells in patients with ENKTCL [57]. Moreover, the expression level of soluble PD-L1 after treatment is a useful biomarker for monitoring patients with minimal residual disease [58].

Targeting PD-1/PD-L1 for the treatment of r/r ENKTCL has a good effect. Nivolumab therapy has been proven to be effective for ENKTCL [59]. A clinical trial of nivolumab in the treatment of three cases of r/r ENKTCL demonstrated a complete response in two patients and a partial response in one patient. Targeting PD-1 has also been proven to be effective for r/r ENKTCL for which treatment with L-asparaginase had failed [60]. In a retrospective case report, seven patients with r/r NKTCL achieved an objective response rate of 100% after seven treatment cycles [60]. The therapeutic effects of other drugs subjected to clinical trials were not as good as those of nivolumab and pembrolizumab. In a phase II trial, avelumab achieved a complete remission rate of 24% and an overall response rate of 38% in the treatment of 21 patients with r/r ENKTCL [61]. A clinical trial (NCT03228836) of IBI308 in the treatment of 28 patients with r/r ENKTCL revealed a progression-free survival period of 30 months.

A study showed that the use of targeting PD-1 and pegaspargase, gemcitabine, and oxaliplatin (P-GEMOX) as a combination therapy for the treatment of nine patients with advanced ENKTCL achieved significant remission in eight patients, including complete remission in seven and partial remission in one [62]. A clinical trial of sintilimab combined with chidamide in the treatment of 41 patients with r/r ENKTCL revealed an objective response rate of 58.3%, a complete response rate of 44.4%, and a partial response rate of 13.9% [63]. These results show that sintilimab also has a beneficial effect in combination therapies.

Leukemia

(1) Acute myeloid leukemia

Most patients with AML can achieve complete remission after conventional chemotherapy, and allogeneic hematopoietic stem cell transplantation is the only treatment option for AML [64]. In recent years, the development of targeting PD-1/PD-L1 has also made significant achievements in the treatment of AML.

Studies have shown that the PD-1 pathway is abnormally expressed in AML. Mouse leukemia cell C1498 expresses low levels of PD-L1 when cultured *in vitro* but expresses elevated PD-L1 levels when cultured *in vivo*, which suggests that the PD-L1 expressions in leukemia cells benefit from the tumor microenvironment [65]. Clinical data also support the dysregulation of the PD-1 pathway in AML. Compared with healthy people, patients with AML have significantly higher PD-1 expression levels on T cells [66]. In addition to the PD-1 pathway, CTLA-4 and TIM-3 [2] are also involved in the pathogenesis of AML.

Clinical trials are ongoing to determine the effectiveness of targeting PD-1/PD-L1 for the treatment of AML, and its individual and combination treatments have shown positive results. A clinical trial showed that the use of nivolumab monotherapy as maintenance treatment in 14 patients with AML (not eligible for transplantation) achieved 6- and 12-month complete remission rates of 79% and 71%, respectively [67]. A phase II clinical study showed that the objective remission rate of nivolumab combined with azacytidine in the treatment of r/r AML was 33% [68]. A clinical trial (NCT02464657) of idarubicin and cytarabine with nivolumab for the treatment of myelodysplastic syndrome and AML showed a relapse-free survival time of 18.54 months (range, 8.20–23.22 months) and an overall survival time of 18.54 months (range, 10.81–28.81 months).

A clinical trial (NCT02708641) of pembrolizumab in the treatment of 12 patients with AML showed a relapse time of 12.14 months. A clinical trial (NCT02996474) of pembrolizumab combined with decitabine in the treatment of 10 patients with r/r AML demonstrated that the regimen was feasible for all 10 people, indicating that the combined drug effect was better.

(2) Acute lymphocytic leukemia

Little is known about the role of targeting PD-1/PD-L1 in acute lymphocytic leukemia (ALL), and only a few relevant clinical trials have been conducted. Currently, a clinical trial (NCT02879695) of nivolumab and blinatumomab or nivolumab and ipilimumab in the treatment of patients with B-cell acute lymphoblastic leukemia is recruiting participants. A clinical trial (NCT04546399) of nivolumab combined with blinatumomab for the treatment of relapsed B-cell acute lymphoblastic leukemia is also recruiting participants. A phase I trial (NCT02819804) of nivolumab combined with dasatinib in the treatment of patients with ALL [69] was terminated because its efficacy could not be evaluated and analyzed. Another clinical trial (NCT03160079) of pembrolizumab combined with blinatumomab for the treatment of adult r/r B-cell acute lymphoblastic leukemia is also currently recruiting participants, and more related trials can be expected in the future.

(3) Chronic myeloid leukemia

Studies have shown that in chronic myeloid leukemia (CML), PD-L1 expression is upregulated in bone marrow cells, and PD-1 is present on T cells [70]. However, little is known about the effectiveness of targeting PD-1/PD-L1 for CML. Some scholars have shown that the use of antigen-pulsed autologous dendritic cells or direct application of *in vitro* transcribed RNA encoding leukemia-related antigens combined with targeting PD-1 may help obtain a stronger immune response and better clinical results [71].
A clinical trial (NCT02011945) of nivolumab combined with dasatinib in the treatment of 16 patients with CML showed no incidence of dose-limiting toxicity. A clinical trial (NCT03516279) of pembrolizumab, dasatinib, and imatinib mesylate or nilotinib for the treatment of CML is currently conducting recruitment, and more related trials are expected in the future.

(4) Chronic lymphocytic leukemia

Ramsay [72] confirmed that the expression of PD-1 on CD3+ cells in patients with chronic lymphocytic leukemia (CLL) was significantly higher than that in healthy individuals. PD-1 expression was found to be a feature of CD4+ and CD8+ T-cell exhaustion in CLL, which inhibits CD4+ and CD8+ T cells from producing certain cytokines (IFN-γ and tumor necrosis factor [TNF]) [73].
However, the efficacy rate of targeting PD-1/PD-L1 for CLL is low. A phase II study (NCT02332980) reported that pembrolizumab was ineffective for CLL but effective for Richter's syndrome (RS) because patients with RS have higher PD-L1 expression levels and low T-cell receptor clonality [74]. Currently, two trials (NCT03153202 and NCT03514017) of pembrolizumab combined with ibrutinib in the treatment of patients with CLL are conducting recruitment. However, no clinical trial (NCT04781855) of the combination of ipilimumab, ibrutinib, and nivolumab for the treatment of CLL has yet been conducted. A clinical trial (NCT03884998) of copanlisib combined with nivolumab in the treatment of patients with NHL in CLL is currently recruiting. Research on immunotherapy for patients with CLL is still ongoing, and more data to guide treatment needs must be confirmed through further research [75].

Multiple myeloma

Studies have shown that the expression level of PD-L1 in plasma cells is different. Its expression level in patients with MM was higher than those in healthy volunteers and patients with monoclonal gammopathy of undetermined significance. In r/r MM, the expression level of PD-L1 is significantly increased [76]. Similar to that in CHL, the protein expression level of PD-L1 in myeloma cells is related to the increase in the PD-L1 copy number. Studies have shown that targeting PD-1 can improve survival in myeloma mouse models [77]. Unlike PD-L1, PD-L2 is not expressed in myeloma cells [78].
In a phase I study, 27 patients with r/r MM were treated with nivolumab, with a median follow-up time of 65.6 weeks, and 17 patients (63%) had the best remission rate [36]. A phase II study (NCT02612779) used nivolumab combined with elotuzumab in the treatment of six patients with MM and showed a progression-free survival time of 16.7 months and an objective remission rate of 51.5%, which were not better than those with monotherapy. Some clinical trials are also underway, such as that of nivolumab combined with melphalan for the treatment of MM (NCT03292263) and nivolumab, carfilzomib, dexamethasone, and pelareorep combined with r/r MM (NCT03605719).
A phase I study showed 20 patients (50%) experienced remission of r/r MM after treatment with pembrolizumab combined with lenalidomide and low-dose dexamethasone [79]. At present, this treatment method is not mentioned in the treatment guidelines for MM, and only a few related clinical trials have been conducted. Thus, more research and exploration are needed in the future.

Adverse reactions

Although targeting PD-1/PD-L1 has remarkable efficacy, it also induces immune-related AEs (irAEs). In principle, all checkpoint inhibitors can potentially induce irAEs in any organ, which can occur late after therapy initiation but possibly also after therapy cessation [80]. As for targeting PD-1/PD-L1, related irAEs can involve the skin, gastrointestinal tract, liver, and endocrine system and other organ systems [81].
irAEs occur for many reasons, which may be related to the increase in cytokine production [82]. However, the types of specific cytokines and their exact roles in the development of irAEs remain unclear, requiring further research. irAEs may also be caused by the cross reaction of T cells and similar antigens on healthy cells [83]. When treating two patients with fatal fulminant myocarditis and rhabdomyolysis, Johnson *et al*. examined the cross-reactivity theory of the etiology of irAEs and found that one or more targets of each patient's anti-tumor immune response were the same as or similar to the antigens normally expressed in the skeletal muscle and myocardium [84].
Most observed irAEs were successfully treated with systemic corticosteroids, but this was not always the case [83]. Hofmann *et al*. retrospectively reviewed cases with irAEs due to nivolumab or pembrolizumab treatment and found that some of these events resolved without treatment, improved with corticosteroid or other treatments, or were not resolved [81]. In addition, Horvat *et al*. recommended that the threshold for starting systemic corticosteroids should be low, and if the symptoms do not improve, the threshold for upgrading the treatment to anti-TNF-α drugs should be considered within 1 week after treatment with high-dose corticosteroids [85].

Conclusions

In summary, targeting PD-1 and PD-L1 can block the combination of PD-1 and PD-L1 to enhance the immune response. It has many applications in tumors and is used in clinical immunotherapy for various tumors, with satisfactory therapeutic effects. In addition, with the gradual advancement of research and the increase in technical level, the therapeutic range of targeting PD-1/PD-L1 in tumors has gradually widened, and the remission rate of the disease has gradually increased. However, this treatment method still faces problems such as high drug development costs, instability, potential side effects, and a lack of standardized PD-1 detection procedures. We believe that with the advancement of research and the improvement of the technical level, these issues will be solved or improved. Targeting PD-1/PD-L1 will achieve greater breakthroughs and exert greater value in clinical research and antitumor therapy in the future.

Abbreviations	
AE	adverse events
ALL	acute lymphocytic leukemia
AML	acute myeloid leukemia
APCs	antigen presenting cells
BICR	blinded independent central review
BV	brentuximab vedotin
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CTLA-4	Cytotoxic-T-lymphocyte-antigen-4
DC	dendritic cel
DLBCL	diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
EHA	The European Hematology Association
ENKTCL	extranodal NK/T cell lymphoma
Fc	crystallizable fragment
FDA	Food and Drug Administration
FL	follicular lymphoma
GCB	germinal center B-cell-like
GVD	gemcitabine, vinorelbine, liposomal doxorubicin
HL	Hodgkin lymphoma
IFN γ	interferon γ
IHC	immunohistochemistry
IL-2	interleukin-2
irAEs	immune-related adverse events
IRC	independent review committee
ITIM	immunoreceptor tyrosine-based inhibitory motif
ITSM	immunoreceptor tyrosine-based switch motif
JNK	Janus N-terminal Kinase
Lag-3	lymphocyte-activation gene 3
LMP1	latent membrane protein 1
LPS	lipopolysaccharide
MCL	mantle cell lymphoma
MDS	myelodysplastic syndromes
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NGCB	non-germinal center B-cell-like
NHL	non-Hodgkin's lymphoma
NK	natural killer
NKTCL	NK/T cell lymphoma
NOS	not otherwise specified
NSCLC	non-small cell lung cancer
PCNSL	primary central nervous system lymphoma
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 2
PD-L2	programmed cell death-ligand 1
PD-Ls	programmed cell death-ligands
P-GEMOX	pegaspargase, gemcitabine, oxaliplatin
PKC-θ	protein kinase C-θ
PMBCL	primary mediastinal large B cell lymphoma
PTCL	peripheral T cell lymphoma
PTL	primary testicular lymphoma
r/r HL	relapsed/refractory HL
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
RGMb	rejection guiding molecule b
RS	Richter's syndrome
SHPs	Src homology 2 domain-containing phosphatases
TCL	T cell lymphoma
TCR	T-cell receptor
TFH	follicular helper T cells
TILs	tumor-infiltrating lymphocytes
TIM-3	T cell immunoglobulin and mucin-domain containing-3
TLR	Toll-like-receptor
TNF	tumor necrosis factor
ZAP70	zeta-chain-associated protein kinase 70

Declarations

Author contributions: Liang Wang designed the study. Wanying Zhao and Yuanzheng Liang collected all the literatures and analyzed the data. Wanying Zhao wrote the paper. All authors revised the paper and approved the publication of this paper.

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