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New Way in Cancer Therapy: PD-1 Inhibitors and Hematologic Diseases

INVITED REVIEW

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ABSTRACT

Programed death-1 (PD-1) is an immune checkpoint pathway used by cancer cells to evade the anti-cancer activity of T cells. If this pathway is active, inhibitory signals create an unresponsive state, bringing about the tumor growth. Nowadays, the PD-1/PD-L1, L2 inhibitor therapy shows a new way of treatment to clinicians who are working with hemato-oncologic cancers. Some diseases, such as classic Hodgkin lymphoma (cHL) and primary mediastinal large-B-cell lymphoma, that express large amounts of programed death-ligand 1(PD-L1), may be a good target of such a therapy. In hematology, the anti-PD-1 therapy is used successfully and safely in cHL. Other studies are limited, or the results are not available yet. Although most of the diseases, except chronic lymphocytic leukemia and multiple myeloma, show meaningful responses, when using these drugs, we must carefully monitor autoimmune and rare, but serious side effects. In this paper, we emphasize the use of PD-1 inhibitors in hematology.

Keywords: PD-1 inhibitor, hematologic disease

INTRODUCTION

The immunotherapy has advanced in recent years. Immune check point inhibitors (ICIs), which can increase the T-cell cytotoxic activity and then lead to the tumor cell lysis (1), have altered dramatically the forms of anticancer therapy.

Coordinated expression of stimulatory and inhibitory signals regulates the hemostasis of the immune system. There are two well-defined inhibitory signal axes: the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programed death receptor 1 (PD-1). The CTLA-4 has a higher binding affinity for CD28 and CD86 compared to CD28. This antigen is expressed on active T cells and regulatory T cells (Tregs), and it is a CD28 homolog (1). When overexpressed, it competes with CD28 to bind to CD80/CD86 on APCs, thus inducing the T-cell anergy (2). Another important immune checkpoint, PD-1, our review's topic, is expressed on the surface of active T cells during the beginning of activation. The PD-1-to-PD -ligand 1 (L1)/PD-L2 ligation reduces their stimulatory pathways and establishes a balance between the T-cell activation and healthy tissue destruction, thereby maintaining the peripheral tolerance. An inadequate immune response results in a prolonged antigenic stimulation, leading to the elevation of PD-1 and subsequent T-cell exhaustion.

Drugs developed for the PD-1/PD-L1, L2 axis can be divided into two groups: anti-PD-1 receptor (nivolumab, pembrolizumab, pidilizumab, etc.) and anti-PD-L1, L2 ligands (durvalumab, atezollizumab, etc.).

Summary of PD-1/PD-L1 Pathway in Lymphomas

Recently, the PD-1/PD-L1 expressions have been evaluated in various hematological malignancies. The results have demonstrated promising results that could change the daily practice.

Morphological diagnostic characteristic of Hodgkin lymphoma (HL) is the presence of Hodgkin and the Reed–Sternberg cells residing in the extensive inflammatory surroundings. In classical HL (cHL) cell lines and primary human samples, the Reed–Sternberg cells express large amounts of PD-L1, and tumor infiltrating lymphocytes (TILs) express PD-1 (3).

The PD-L1 expression rates in primary mediastinal large-B-cell lymphoma (PMBCL) varies from 36% to 100% according to studies. Jak-2, CIITA (MHC class 2 transactivator encoding), and REL (encoding of a NF-KB subunit) genetic rearrangements are also seen in PMLBCL, supporting the immunosuppressive state with the PD-1/PD-L1 axis (4, 5). Jak-2 is encoded in the 9p24.1 gene locus. Jak-2 also causes an increase in the PD-L1 expression using signal transmission pathways. Genetic mutations 9p24.1 regulate the increase of PD-L1 and PD-L2. In the PMBCL animal model, the JAK-2 inhibition decreases tumor growth. Decreased CIITA protein levels mean the

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reduction of the MHC class 2 on the cell surface, so that the antigen presentation will be defective. An increased NF-KB expression results in an induced PD-L1 expression.

Diffuse large-B-cell lymphoma (DLBCL) is divided into two subgroups, based on the cell origin: germinal center B-cell-like (GCB) and activated B-cell-like (ABC) or non-GCB. The ABC-DLBCL has a bad prognosis. Andorsky et al. reported the PD-L1 expression in 1 out of 19 (5%) patients with the GCB type, and 8 out of 14 (57%) patients with the ABC type in 2011 (6). Contrast studies are reported about a higher PD-1 expressing the TILs level, whether in the GCB versus ABC subtype (7, 8). A tumor PD-L1 positivity is associated with a poor prognosis, B symptoms, elevated IL2 receptors, and a higher IPI score (8). Lower soluble PD-L1 (<1.52 ngr/ml) levels were associated with shortened survival (76% vs. 89% p>0.001) (9). An EBV-positive DLBCL represents 76%–100% of PD-L1 expressions (10, 11). Similarly, 73% of primary EBV+PTLDs cases (19 out of 26 cases) had expressed PD-L1 (12). These observations emphasize that the PD-1 signal pathway may cause tumor immune escape in EBV-associated tumors.

In follicular lymphoma, contrasting study results have been published up to date: PD-1 positive T cells and CD14+follicular dendritic cells are said to be independent predictors of transformation of follicular lymphoma. PD-1 and PD-L1 are rarely expressed by follicular tumor cells, but PD-1 is highly expressed at the germinal center follicular cells, and even lymphoma TILs have increased PD-1 when compared with peripheral T cells (13). Carreras et al. showed an improved survival in follicular lymphoma with increased PD-1+TIL and T reg-cells, as opposed to solid tumors that have shortened survival (14). Richendolar et al. demonstrated that the PD-1+follicular helper T-cell number raises as an independent prognostic marker of decreased survival (15).

Burkitt lymphoma cells do not have the PD-L1 expression, so this type of lymphoma does not seem to be affected by anti-PD-1 treatment (6).

Multiple myeloma plasma cells have more PD-L1 expression than healthy individuals or patients with MGUS (16).

Application of PD-1 Inhibitors in Lymphoma and Other Hematologic Malignancies

The check point inhibitor therapy has been more studied in patients with relapsing or refractory (r/r) cHL and PMLBCL to date.

Results of the pivotal Phase 1 CheckMate 039 study, which included 23 r/r cHL patients, were promising. An overall response rate (ORR) to nivolumab was 87%, with 4 patients showing complete response (CR; 17%) (Table 1) (17). In another Phase 1 study, KEYNOTE-013, pembrolizumab in HL relapsed after BV, the ORR was 65%, with 5 patients showing CR (16%) and 15 patients showing partial response (PR; 48%). Interestingly, the pemprolizumab ORR was lower in prior allogeneic stem cell transplantation (ASCT) naive patients (44% vs. 73%) (18).

In June 2016, the Food and Drug Administration (FDA) approved nivolumab for the treatment of relapsed/refractory (r/r) cHL.

A multicenter, multicohort, single-arm Phase 2 trial named CheckMate 205, which included 80 patients with r/r HL, showed better results than expected. All patients were treated with ASCT and BV prior to nivolumab. After the median follow-up of 8.9 months, the ORR was 66%. Six months later, the PFS was 77%, with an overall survival of 99% (19). The Phase 2 KEYNOTE-087 study of pembrolizumab had the following three cohorts: patients which relapsed and/or refractory disease after ASCT and following brentuximab vedotin therapy (Cohort 1); patients who did not respond to chemotherapy, who were ineligible for ASCT, and who had progressive disease after brentuximab vedotin therapy (Cohort 2); and patients with relapsed and/or refractory disease after ASCT, but who had not received post-ASCT treatment as brentuximab vedotin (Cohort 3; ORR 80%) (20).

According to Turkey real-life experience, 75 retrospective patient analyses showed nearly the same efficacy as in other studies. The ORR was 64% with 16 complete responses (CR 22%) after 12 weeks (21). The results of the CheckMate 205, an extended follow-up multicohort single-arm Phase 2 study, were promising. The overall responses ranged between 65% and 73% in all the groups with r/r HL (22).

The number of human studies is limited because of an increased risk of acute graft versus host disease (GVHD) and the GVHD-related mortality with PD-1 blockade after or before the allogeneic HSCT has been demonstrated in murine models. In a one-sample study from El Cheik et al., out of 9 patients with HL who received nivolumab prior allo-SCT, all of them had Grade 2 to Grade 4 acute GVHD. The ORR was 77% with 3 out of 9 CR (33%), and 4 patients had PR (44%) (23). A retrospective analysis of nivolumab anti-PD-1 after allo-HSCT evaluated the efficacy and safety in 20 patients with HL. The ORR was 95% CR, and the PR rates were 42% (n=8) and 52% (n=10), respectively. Drug-induced GVHD was found in 6 patients, and 2 patients died from GVHD (24).

After nivolumab showed success and safety, it was combined with other older drugs such as AVD in a Phase 2 study (25). It is used in patients aged >60 years, who cannot receive standard chemotherapy, combined with BV (26). There is an undergoing trial investigating the combination of PD-1 inhibition with brentixumab as well as CTLA-4 blockers in a r/r disease (27).

Anti-PD-1 therapy is shown to be less effective in B-cell lymphomas. In a Phase 1 nivolumab study including 11 patients with DLBCL, the ORR was 36% (1 CR 9%) 3 patients 27% PR (28). Another PD-1 inhibitor, pidilizumab, showed no response. Moreover, in 2 patients, the disease had progressed (29). A large international Phase 2 study of pidilizumab conducted on 66 patients with measurable disease after ASCT showed good outcomes with 51% ORR (34% CR, n=12; PR 17%, n=6) (30). This improved response may be associated with a post-ASCT state, which shows remodeling of the immune system and alterations of the lymphoid subsets. And further study will show whether post-ASCT residual disease is an ideal setting for immune check point blockade.

It has been shown that a high number of PD-1+TILs is associated with an improved survival in follicular lymphoma (FL) (31). The first study examined these patients with FL treated with pidilizumab monotherapy, and CR was found in only 1 patient (29). Another Phase 1 study used nivolumab in 10 patients with FL, and ORR was 40% (1 CR and 3 PR) (28). A combination of rituximab with

Table 1. Some studies examining anti-PD-1 drugs in hematological diseases and their response rates

Disease	Phase	Drug	Population	Number of patients	Response	Adverse events >10%
r/r HL	Phase 1 (18)	nivo	78% after ASCT, 78% BV	23	ORR 87% CR17% PR 70%	Rash 22% Decreased platelet count 17%
r/r HL	Multicohort single-arm Phase 2 (19)	nivo	Failure after ASCT+BV	80	ORR 66%	Fatigue 25% IRR 20% Rash 16%
r/r HL	Extended multicohort single-arm Phase 2 (22)	nivo	BV naive (Cohort A); BV after auto-HCT Cohort B); BV before and/or after auto-HCT (Cohort C)	63 80 100	ORR 69% 65% 73%	Fatigue 23% Diarrhea 15% IRR 14%
r/r HL	Phase 2 (20)	pemb	Autologous SCT followed by BV (Cohort 1), salvage chemotherapy followed by BV (Cohort 2), autologous SCT (Cohort 3)	210	ORRs were 73.9% (Cohort 1), 64.2% (Cohort 2), 70.0% (Cohort 3)	Immune-response-related events 28% Hypothyrodism 12% Pyrexia 10%
r/r DLBCL	Phase 1 (28)	nivo		11	ORR 36% PR 18% CR 18% SD 27%	
r/r PMBCL	Phase 1b (44)	pemb		17	ORR 41% SD 35%	
r/r FL	Phase 1 (28)	nivo		10	ORR 40% CR 10% PR 30% SD 60%	

HL: Hodgkin lymphoma; DLBCL: Diffuse large-B-cell lymphoma; PMBCL: Primary mediastinal large-B cell lymphoma; FL: Follicular lymphoma; BV: Brentuximab vedotin; ORR: Overall response rate; CR: Complete response; PR: Partial response; IRR: Infusion-related reaction; nivo: Nivolumab; pemb: Pembrolizumab

PD-1 inhibitor therapy, a Phase 2 study included 32 r/r FL patients. Twenty-nine patients were evaluated for response, and ORR was 19 (66%) with 15 showing CR (52%) and 4 showing PR (14%) (32). These data indicate improved responses compared to those re-treated with rituximab only (ORR 66% vs. 40% and CR 52% vs. 11%, respectively) (32, 33). However, peripheral CD4+ and Cd8+ T-cell PD-L1 expression was higher in responders, and the PD-L1 expression by FL cells does not seem to be the main pathogenetic factor of disease unlike solid tumors and CHL. In this research, r/r four Mantle cell lymphoma patient had no response (32).

In 2 CLL cases, there was no response to nivolumab monotherapy (28). In a Phase 2 study examining the nivolumab with ibrutinib combination, 8 of 12 patients had PR as best response (34).

In HIV-associated lymphoma, the PD-1 expression is increased in HIV-specific CD8+ T cells that have an impaired function, and an invitro blockage of the PD/PD-L1 axis leads to an increased survival, proliferation, and cytokine secretion (35). The PD-1 expression is higher in HIV-infected patients and those who have progressive disease. PD-L1 is also increased on the B cells of HIV-infected individuals. It is said that the elevated PD-L1 level on the germinal center B-cell may be responsible for lymphomagenesis in HIV-infected patients. Because of a low number of CD4+ T cells, HIV-infected lymphoma patients have an increased risk of febrile neutropenia and opportunistic infection. Thus, anti-PD-1 inhibitor therapy seems to be a suitable treatment option in patients who are not eligible for cytotoxic chemotherapy.

Unlike the relatively rapid responses of conventional chemotherapy, the response to ICI treatment is often delayed, leading to a misleading diagnosis of disease progression. Therefore, it is doubtful whether monotherapy with ICI is appropriate in patients with a more aggressive lymphoma, such as Burkitt's lymphoma.

More than 40% of patients respond after 8 weeks. Limited data

from the Phase 1b study by Lesokhin et al. in 27 r/r multiple myeloma patients, showed a stable disease in 17 patients (63%) as a best response (28). Huang et al. classified patients after autologous transplantation with their serum levels of soluble PD-L1 as high or normal plus low. High levels were associated with shorter duration of response as an independent risk factor (36). Thirteen of 17 patients responded to the pembrolizumab+lenalidomide treatment, according to a Phase 1, multicenter, nonrandomized, dose-escalation trial, KEYNOTE-023. The ORR was 76%, with a very good CR in 4 patients, and a PR in 9 patients (37). The first Phase 2 trial investigated the PD-1 inhibitor (pembrolizumab) and IMID (pomalidomide) efficacy in 48 patients. Results were promising with an ORR at 60% and sCR/CR in 4 (8%) patients, VGPR in 9 (19%), and PR in 16 (33%) (38). But the pembrolizumab combination Phase 3 studies were stopped by FDA in July 2017 due to more deaths and side effects (39).

Patients newly diagnosed with acute myeloid leukemia do not have expressed PD-L1. Thus, studies probably used this drug as a combination with a hypomethylating agent for a possible synergistic effect. In a study examining the use of nivolumab combined with 5-azasitidin in r/r AML or older patients with AML (>65 years), the ORR was 34% (18/53 pts), and the CR and CR insufficient count recovery was 21% (11/53 pts) (40). As opposed to AML, the MDS patients had an increased expression of PD-L1, and hypomethylating-agent-resistant MDS patients had a higher expression of PD-L1 (41). Nivolumab, when applied as a single drug, did not show any clinical activity, and ipilizumab, another PD-1 inhibitor, had 2 responders of 2 patients (41). A combination with azasitidine may be more useful in this group of patients, where the ORR raises to 69% (6/11) (42). In future, patients with AML will be treated according to their gene profile. There are many drugs from this field that have been approved or are under investigation (43). We can consider application of this drugs class or ICIs in elderly patients or those who are not suitable for conventional chemotherapy.

CONCLUSION

Important studies on ICI in the treatment of lymphoma are generally associated with PD-1 inhibitors, and to the best of our knowledge, there are no serious studies on the use of anti-PD-L1 therapy present in the literature. With immune checkpoint signal blocking, normal cells can be damaged in addition to tumor cells. This group of drugs should be used with caution, although it may appear to have an acceptable safety profile. The ICI treatment has found its place in the current practice, especially in the treatment of r/r cHL and PMBCL, out of hematologic diseases. In the studies on lymphoma subtypes other than cHL and other hematological malignancies, the number of samples is small, hence large prospective studies will show us the path in this new field.

Adverse Events

According to a large cohort study by Armand et al., the most common any-grade drug-related adverse effects were fatigue, diarrhea, and infusion-related reactions at 23%, 15%, and 14%, respectively; the most common Grade 3 to Grade 4 drug-related adverse effects were increased lipase 5% and ALT (3%) levels, and neutropenia (3%) (22).

With pembrolizumab, the most common were immune-mediated adverse effects, seen at a rate of 28.6%, followed by hypothyroidism 12.4% and pyrexia 10.5% (20).

Other rare but important adverse reactions that lead to discontinued application of anti-PD-1 drugs were pneumonitis (2%) and autoimmune hepatitis (1%) (22).

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