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Prognostic and clinicopathological significance of PD-1/PD-L1 expression in the tumor microenvironment and neoplastic cells for lymphoma

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ABSTRACT

Background: Recently, unprecedented clinical efficacy was observed during treatment of many solid tumors because of the introduction of programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) immune checkpoint inhibitors. Preliminary clinical data indicates that checkpoint inhibition also represents a promising therapeutic strategy for certain lymphoid malignancies. However, PD-1/PD-L1 expression levels on neoplastic cells and in the tumor microenvironment vary among subtypes and their prognostic implications remain uncertain.

Main body: Here, we review the clinicopathological significance of PD-1/PD-L1 expression in lymphomas. Increased infiltration of PD-1 + tumor-infiltrating lymphocytes (TILs) is a favorable prognostic factor in diffuse large B-cell lymphoma (DLBCL) but not in Hodgkin's lymphoma (HL). Higher numbers of PD-1 + TILs were observed in follicular lymphoma (FL) than in other subtypes of B-cell lymphoma; however, its prognostic significance remains controversial. Infiltration of PD-L1 + immune cells showed a trend toward better overall survival in nasal natural killer (NK)/T-cell lymphoma and adult T-cell leukemia/lymphoma, more likely to be classified as activated macrophages and dendritic cells in microenvironment but its biological effect is not clarified. Peripheral PD-1 + T cells could be detected in blood samples from DLBCL and chronic lymphocytic leukemia (CLL) and correlated with disease progression and poor prognosis. PD-1 + neoplastic T cells were more frequently observed in cutaneous T-cell lymphoma, including Sézary syndrome and mycosis fungoides, which may be involved in the progression of epithelial-derived T lymphoma. Studies on PD-L1 expression in neoplastic cells mostly focused on DLBCL. PD-L1 + neoplastic cells were observed only in a small subset of DLBCL, mainly associated with activated B cell (ABC) subtypes and Epstein-Barr virus (EBV) positivity; however, its prognostic role remains controversial. In either T or B lymphoma, elevated serum or plasma levels of soluble PD-L1 represent adverse prognostic factors. Notably, in clinical trials of classical HL, the frequency of 9p24.1 chromosome alterations increases the abundance of PD-1 ligand expression, appearing to predict responses to anti-PD-1/PD-L1 therapy. The cytogenetic alterations affecting chromosome 9p24.1 including the *CIITA* rearrangement were also frequently observed in certain specific subtypes of large B-cell lymphomas.

Conclusions: The clinical roles of PD-1/PD-L1 expression vary between subtypes of lymphoma. Future studies should delineate the prognostic and predictive roles of PD-1 and PD-L1 expression.

Abbreviations: PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; TILs, tumor-infiltrating lymphocytes; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; FL, follicular lymphoma; NK, natural killer; CLL, chronic lymphocytic leukemia; EBV, Epstein-Barr virus; cHL, classical Hodgkin's lymphoma; OS, overall survival; IFN-γ, interferon gamma; PFS, progression free survival; IHC, immunohistochemistry; T_{FH}, T follicular helper; MZL, marginal zone lymphoma; MCL, Mantle cell lymphoma; SLL, Small lymphocytic lymphoma; CLL, chronic lymphocytic leukemia; ROC, receiver operating characteristic curve; ATLL, adult T-cell leukemia/lymphoma; EFS, event-free survival; HTLV-I, human T-cell leukemia virus type-I; qRT-PCR, quantitative real-time reverse transcriptase PCR; CTCL, cutaneous T-cell lymphoma; SS, Sézary syndrome; MF, mycosis fungoides; E-MF, erythrodermic mycosis fungoides; ALCL, anaplastic large cell lymphoma; PMBL, Primary mediastinal (thymic) large B-cell lymphoma; HHV8, human herpes virus 8; PTCL, peripheral T-cell lymphoma; ALK, anaplastic lymphoma kinase; NNKTL, nasal NK/T-cell lymphoma; sPD-L1, soluble form of PD-L1; ELISAs, enzyme-linked immunosorbent assays; NHLs, non-Hodgkin lymphomas; PMBCL, primary mediastinal large B-cell lymphomas; PTL, primary testicular lymphoma; PCNSL, primary central nervous system lymphoma; DSS, disease specific survival; SVs, Structural variations; ZAP-70, zeta chain of T cell receptor associated protein kinase 70

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1. Introduction

The programmed cell death 1 (PD-1)/programmed cell death ligand 1(PD-L1) pathway is an immune checkpoint pathway that plays an important role in the maintenance of self-tolerance and the control of excessive immune responses. However, in tumor cells, this pathway is utilized to suppress anti-tumor immune responses and to evade immune surveillance [1]. PD-1 is predominantly expressed on activated T cells, B cells, and natural killer (NK) cells, while the PD-1 ligands PD-L1 [2,3] or PD-L2 [4] are expressed on various immune cells (including macrophages, dendritic cells, and lymphocytes) and tumor cells [5,6]. After binding to PD-1 ligands, PD-1 transmits inhibitory signals to attenuate T cell proliferation and function, leading to T cell exhaustion [1].

In recent years, immunotherapies using PD-1 or PD-L1 blockade have been used to enhance anti-tumor immune responses [1] and to obtain beneficial therapeutic effects with an acceptable safety profile in solid tumors [7–9]. Preliminary data has also shown therapeutic activity of PD-1 blockade in certain hematological malignancies, including classical Hodgkin's lymphoma (cHL) and follicular lymphoma (FL), as well as potential utility in diffuse large B cell lymphoma (DLBCL) [10–12]. PD-L1 expression has been associated with clinical response to PD-1 checkpoint inhibition in many cancer types. In addition, patients with high PD-L1 expression in tumor-infiltrating immune cells showed better therapeutic responses and clinical outcomes [13–16]. However, in the case of lymphoid malignancies, the situation is more complex. 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. Moreover, previous studies on the prognostic influence of PD-1 + tumor-infiltrating lymphocytes (TILs) in malignant lymphoma have generated conflicting results [17–19]. The expression of PD-1 and PD-L1 and their clinical role in lymphoma need to be better understood. In this review, we provide a summary of current studies on the expression of PD-1 and PD-L1 in lymphoid malignancies.

2. PD-1 + tumor-infiltrating lymphocytes

The presence of PD-1 + TILs is a proven prognostic indicator for different tumor entities [20,21]. A number of studies have demonstrated significantly increased numbers of PD-1 + TILs in HL and B-cell lymphomas (Table 1). In a study of 189 patients with cHL, the number of PD-1 + TILs was a median of 27 cells/mm^2 and a mean of 269 cells/mm^2, being higher in the lymphocyte-rich subtype and lower in the mixed cellularity variant. PD-1 + rosettes around neoplastic cells were observed in all three cases of nodular lymphocyte-predominant HL, but were rare in cHL (only 1%). With a cut off score of 23 cells/mm^2, an increased amount of PD-1 + TILs was a stage-independent negative prognostic factor of overall survival (OS) in cHL [19]. Another study showed that PD-1 levels were elevated in TILs in three patients with HL compared with healthy volunteers, and blockade of the PD-1 signaling pathway restored the interferon gamma (IFN-γ)-producing function of TILs *in vitro* [22]. However, in a study of patients with 18 cHL, PD-1 expression was significantly lower in the tumor microenvironment, which might imply a low expression of PD-1 in TILs [23].

In contrast to cHL, a number of studies have found that PD-1 + TILs are a favorable prognostic factor in DLBCL [24–26]. In a study of 76 Chinese patients with DLBCL, PD-1 was expressed in the TILs of 39.5% of the patients, being significantly higher in male patients and in patients without B symptoms. PD-1 + TILs were shown to be related to prolonged OS of patients with DLBCL [26]. Other studies found that increased amounts of PD-1 + TILs were associated significantly with prolonged OS [24,25] and progression free survival (PFS) [25] in DLBCL, and represented a favorable prognostic factor for OS and PFS, independent of international prognostic index, B symptoms, and Choi classification [25]. A number of studies have examined the prognostic effects of PD-1 + follicular helper T-cells in FL and showed inconsistent results. Smeltzer et al. analyzed 58 FL biopsy samples using multicolor immunohistochemistry (IHC) and flow cytometry, and found that PD-1 + cells represented two separate populations, T follicular helper cells (T_{FH}) and exhausted T cells. The staining pattern of PD1 + cells, rather than their quantity was predictive of outcomes. PD1 + cells with diffuse staining were associated with a shorter time to transformation and inferior OS compared to those of PD1 + cells localized to the follicles [27]. However, in another study of 91 patients with FL, increasing amounts of PD1 + cells (> 35.6 cells/high power field) were proven to be an independent poor prognostic factor for OS [18]. In contrast to the above studies, other studies have confirmed that elevated levels of PD1 + cells favor the outcomes of FL [17,28]. In a large study, Carreras et al. analyzed 100 newly diagnosed patients with FL as well as 32 patients at first relapse. The median percentage of PD-1-positive cells was 14% at diagnosis, being lower in patients with grade 3 FL, poor performance status, and high serum lactate dehydrogenase levels. A high content of PD1 + cells predicted favorable OS (5-year OS was 20%, 46%, and 48% when the PD1 + cell percentage was < 5%, 6–33%, > 33%, respectively), whereas a marked reduction was observed in transformation [17]. Nevertheless, other studies suggested that there was no correlation between the PD-1 + T-cells and prognosis, including OS [29,30] and the time to treatment failure [30]. Only in the male subgroup, high levels of PD1 + cells (≥14.4%) were observed to worsen PFS [29]. Muenst and colleagues examined the distribution of PD-1 + TILs in 403B cell lymphomas cases, mainly comprising primary or secondary DLBCL, FL, extranodal marginal zone lymphoma (MZL), Mantle cell lymphoma (MCL), Small lymphocytic lymphoma (SLL), and chronic lymphocytic leukemia (CLL). The quantitative analysis showed that numbers of PD-1 + TILs were higher in FL, particularly in FL grades 1–2 (mean 6.5%), and extranodal MZL (mean 4.2%); lower in MCL, SLL, CLL, and in secondary DLBCL arising from SLL/CLL and MZL (mean 0.01–1.5%). In receiver operating characteristic curve (ROC) analysis for the prognostic cutoff score, only TILs in FL and secondary DLBCL arising from FL were identified, showing that increasing numbers of TILs greater than 2.8% favor disease-specific survival [28].

In a study of 41 patients with primary cutaneous extranodal NK/T cell lymphoma (ENKTL) [31], Kim et al. evaluated the expression of PD-1 by skin skin-infiltrating cells (both reactive and neoplastic). PD-1 positivity in cutaneous ENKTL was found to differ depending on the clinical morphology: a higher positivity of PD-1 was found in cases with erythematous lesions, which is characterized by a low proliferation index, lack of angioinvasion, and an associated reactive inflammatory background, including small reactive TILs; while a lower positivity of PD-1 was found in cases with nodular lesions, which is mainly composed of large tumor cells. This result seems to suggest that TILs in ENKTL has higher PD-1 expression than tumor cells. Although PD-1 positivity differed depending on the clinical morphology, this did not affect survival outcomes for cutaneous ENKTL. Consistent with the above findings, other studies have confirmed that PD-1 is mainly expressed in tumor-infiltrating immune cells in ENKTL, although the expression rate is relatively low. PD-1 + TILs were observed in only 11.4–20.5% of ENKTL patients, and there was no correlation between the PD-1 + TILs and prognosis [32,33].

3. PD-L1 + immune cells

Currently, only a few studies have focused on the clinical role of PD-L1 + immune cells within the tumor microenvironment in lymphoma (Table 1). In a study of 52 patients with FL, including newly diagnosed and transformed subtypes, PD-L1 was predominantly positive in macrophages. In addition, higher levels of intrafollicular PD-L1 + macrophage infiltration at diagnosis were associated with shorter time to transformation using univariate Cox regression analysis; however, they were not significantly associated with OS or PFS from diagnosis [34].

Jo et al. evaluated the expression of PD-1 and PD-L1 by TILs and tumor cells in 79 ENKTL-nasal type biopsy samples using

Table 1
Clinical significance of PD-1/PD-L1 expression in immune cells.

Biomarker	Author (Year)	Lymphoma (No. of patients)	Cutoff	Sample (Method)	Antibody (manufacturer)	Clinical significance
PD-1+ TIL						
	Muenst et al. (2009) [19]	HL (280)	23 cells/mm^2	Tissue (IHC)	AF1086 (R&D Systems)	An increased amount of PD-1+ TIL was a stage-independent negative prognostic factor of OS as opposed to the number of FOXP3+ regulatory T cells.
	Fang et al. (2017) [26]	DLBCL (76)	NR	Tissue (IHC)	MRQ-22 (SGB-BIO)	PD-1+ TIL was associated with the patients' gender and B symptoms; PD-1+ TIL was related to prolonged OS.
	Kwon et al. (2016) [25]	DLBCL (126)	NR	Tissue (IHC)	MRQ-22 (Cell Marque)	Increased infiltration of PD-1+ TILs was associated with prolonged PFS and OS in DLBCL patients treated with R-CHOP, whereas PD-L1 expression had no prognostic significance.
	Ahearne et al. (2014) [24]	high-grade DLBCL (70)	median	Tissue (IHC and FCM)	NR	PD-1^{high} cell number above the median was an independent prognostic factor with better OS.
	Wahlin et al. (2010) [80]	FL (70)	NR	Tissue (IHC and FCM)	(Spanish National Cancer Research Centre)	CD4+ cells (follicular) were associated with poor outcome and PD-1+ (follicular) and CD8+ cells (interfollicular) were associated with good outcome.
	Smeltzer et al. (2014) [27]	FL (58)	NR	Tissue (IHC and FCM)	NAT (Abcam)	CD14+ cells localized in the follicle were associated with a shorter time to transformation (TTT) and PD-1+ cells with diffuse staining were associated with a shorter TTT and inferior OS.
	Richendollar et al. (2010) [18]	FL (91)	35.6 cells/highpower field	Tissue (IHC)	NAT (Abcam)	PD-1-positive follicular helper T cell correlated with the number of FOXP3+ regulatory T cells and was an independent poor prognostic factor of OS.
	Takahashi et al. (2013) [29]	FL (82)	14.4%	Tissue (IHC)	NAT (Abcam)	Multivariate analysis detected no significant prognostic effect of PD-1-positive cells in OS. In male subgroup, high levels of PD-1-positive cells were found to be a prognostic factor for PFS.
	Koch et al. (2012) [30]	FL (264)	–	Tissue (IHC)	NAT (Abcam)	No correlation between the PD-1+ follicular helper T-cells and the time to treatment failure or OS in patients with advanced stages of FL.
	Carreras et al. (2009) [17]	FL (132)	Median: 14%	Tissue (IHC)	NAT105 (Abcam)	A high content of PD-1-positive cells predicted favorable outcome of FL patients, whereas a marked reduction is observed in transformation.
	Muenst et al. (2010) [28]	B-NHL (403)	> 2.8% or 168 cells/mm2	Tissue (IHC)	AF1086 (R&D Systems)	Increased number of PD-1+ TIL is associated with significantly improved DSS in FL.
	Kim et al. (2017) [31]	Cutaneous ENKTL (41)	positive: > 10%	Tissue (IHC)	NR	The positivity of PD-1 in cutaneous ENKTL differs depending on the clinical morphology of the lesion. PD-1 is mainly expressed in TILs but has no prognostic value.
	Muhamad et al. (2019) [32]	ENKTL (49)	positive: > 5%	Tissue (IHC)	NAT105 (Cell Marque)	PD-1 expression in the stroma cells was positive at a low proportion (only 20.5% patients) and did not predict prognostic outcomes.
PD-L1+ immune cells						
	Keane et al. (2015) [81]	DLBCL (252)	−0.278958829	Tissue (gene quantify)	–	59% of patients had a CD4*CD8:M2*PD-L1 immune ratio above the cutoff and with a higher 4-year overall survival of 75.6%.
	Blaker et al. (2016) [34]	FL (52)	NR	Tissue (IHC)	a Lab Vision Autostainer 480S (Thermo Fisher Scientific Waltham)	High degree of intrafollicular PD-L1+ macrophage infiltration at diagnosis was associated with shorter TTT but not significantly associated with OS or PFS in the rituximab era.
	Jo et al. (2016) [33]	NNKTL (79)	NR	Tissue (IHC)	PD-1(Cell Marque) PD-L1(R&D Systems)	PD-L1-positive patients had a trend toward better OS compared with that in patients with PD-L1-negative in TC and TIL. While PD-1 expression in TC and TIL was not significantly associated with OS rates.
	Muhamad et al. (2019) [32]	ENKTL (49)	positive: > 5%	Tissue (IHC)	E1L3N (CST)	PD-L1 expression in the stroma did not predict prognostic outcomes.
	Miyoshi et al. (2016) [35]	ATLL (123)	miPD-L1(+): < 50% TIL staining and ≥10 PD-L1+ stromal cells	Tissue (IHC)	ab174838 (Abcam)	miPD-L1(+) ATLL (MST 18.6 months) showed superior OS compared with PD-L1(-) ATLL (MST 10.2 months) .

Abbreviations: PD-1, programmed death-1; PD-L1, programmed death ligand-1; TIL, tumor infiltrating lymphocyte; HL, hodgkin lymphoma; IHC, immunohistochemistry; OS, overall survival; DLBCL, diffuse large B cell lymphoma; NR, not report; PFS, progress-free survival; FC, flow cytometry; FL, follicular lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; DSS, disease-specific survival; ENKTL, extranodal NK/T cell lymphoma; NNKTL, nasal NK/T-cell lymphoma; TC, tumor cell; ATLL, adult T-cell leukemia/lymphoma.

immunestaining. The proportion of PD-L1 expression in TILs and tumor cells were 78.5% and 79.7%, respectively; whereas PD-1 in TILs and tumor cells was expressed at a very low level (only 11.4 and 1.3%, respectively). The PD-L1 positivity in TILs and tumor cells was significantly associated with low international prognostic index. Higher levels of PD-L1 + TILs were associated with a trend toward better OS, but did not show a significant statistical difference [33]. In a larger study of 135 patients with adult T-cell leukemia/lymphoma (ATLL), the investigators divided the patients into four subgroups based on the PD-L1 expression in nonmalignant stromal cells of the tumor microenvironment and tumor cells, where 58.5% of patients with the PD-L1-negative expression in tumor cells and abundant PD-L1 expression in stromal cells were considered as miPD-L1(+); the other group, which did not express PD-L1 in any cell, were considered as miPD-L1(−) (34.1%). The miPD-L1 (+) ATLL (median survival time 18.6 months) showed superior OS compared with that in the PD-L1 (−) ATLL group (median survival time 10.2 months) [35].

4. PD-1 expression in peripheral T cells

Previous studies found that PD-1 expression is significantly increased in peripheral blood CD3+ T lymphocytes of patients with HL, CLL, and multiple myeloma. Immunomodulatory therapies, such as lenalidomide or panobinostat, significantly reduced the PD-1 surface expression on the patients' T lymphocytes [36–38]. Recently, some studies explored the relationship between PD-1 expression on peripheral blood CD4+/CD8+ T cells and prognosis in different subtypes of lymphoma (Supplemental Table 1). In CD4+ T cells of patients with DLBCL, the median fluorescence intensity (MFI) of PD-1 was 541.5, which was significantly higher than the 250 measured in healthy controls [39]. The higher percentage of PD-1+ CD4+ peripheral T cells was associated with significantly lower treatment efficiency [40], and poor event-free survival (EFS) and OS [39]. Notably, the PD-1 expression on the surface of peripheral blood CD4+ T cells was not consistent with the PD-1 expression observed from the tumor microenvironment detected using IHC [39]. In CLL and SLL, more peripheral CD8+ PD-1+ and CD4+ PD-1+ cells were present than in healthy volunteers. In particular, CD8+ PD-1+ cells were elevated in relapsed or refractory cases [41]. The higher numbers of peripheral blood CD4+ PD-1+ T cells at baseline was also associated with a significantly shortened time to first treatment [42].

ATLL is a CD4+ CD25+ T-cell malignancy that can be infected by human T-cell leukemia virus type-I (HTLV-I), causing T-cell dysfunction and an immunodeficient state. Shimauchi et al. investigated whether PD-1 was expressed on CD4+ cells (neoplastic or non-neoplastic) or CD8+ cytotoxic cells in peripheral blood from 11 patients with ATLL. The study found that PD-1 was mainly expressed in peripheral blood CD4+ T-cells rather than in CD8+ cells. Moreover, a statistically significant correlation was shown between the absolute number of ATLL tumor cells and the number of PD-1+ CD4+ cells. These findings implied that PD-1 could be used as a marker for ATLL malignant cells [43].

5. PD-1 expression in neoplastic cells

With respect to PD-1 expression in neoplastic cells, more research has focused on T-cell lymphoma than on B-cell lymphoma (Table 2). As early as 2007, a study investigated PD-1 expression in neoplastic cells of multiple subtypes of lymphoma. A series of 161 lymphoma tissues was analyzed using IHC. In B-cell lymphoma, PD-1 was expressed in neoplastic B cells from most nodal SLL and CLL cases (12/13), but only exceptionally in grade III FL (3/3), and in a small proportion of DLBCL (2/25). In T-cell lymphoma, PD-1 expression in neoplastic cells was restricted to the angioimmunoblastic subtype [43]. In blood samples from patients with CLL, PD-1 expression detected by flow cytometry [44] or transcripts detected by quantitative real-time reverse transcriptase PCR (qRT-PCR) [45] confirmed the presence of PD-1 on the CLL cell surface; however, high PD-1 expression in neoplastic cells was not associated with PFS or OS [45].

In recent years, increasing numbers of studies have found that the expression of PD-1 in neoplastic cells is closely related to cutaneous T-cell lymphoma (CTCL). The expression of PD-1 by more than 50% of the neoplastic T cells was noted in 89% cases of Sézary syndrome (SS) (24/27) and in only 13% cases of mycosis fungoides (MF) or erythrodermic mycosis fungoides (E-MF) (8/60) [46]. When the positive definition dropped to 11%, PD-1 positive expression was detected in 84.0% of MF cases [47]. Nguyen et al. found that PD-1 correlated with disease progression in epitheliotropic T cell dyscrasias ranging from minimal staining (14.3%) to significant staining in MF (60.2%), and could used as a means of distinguishing CD30+ MF from primary cutaneous anaplastic large cell lymphoma (ALCL) (PD-1-negative expression) [48]. In Lennert lymphoma, > 20% PD-1 positive neoplastic cells were observed in 53.8% of patients (14/26) and was associated with poor OS using univariate analysis [49]. A number of studies evaluated the expression of PD-1 by neoplastic cells in ENKTL, and found that PD-1 expression was undetectable or rarely expressed in tumor cells. PD-1+ tumor cells were observed in only 0–2.4% of ENKTL patients [32,33,50].

6. PD-L1 expression in neoplastic cells

PD-L1 is not expressed by normal epithelial tissues; however, it is aberrantly expressed on a wide range of human solid cancer cells and is associated with poorer prognosis [51–54]. PD-L1 expression in neoplastic cells has also been reported in certain aggressive lymphomas (nodular sclerosis and mixed cellularity cHL, Primary mediastinal (thymic) large B-cell lymphoma (PMBL), T cell/histiocyte-rich B-cell lymphoma, plasmablastic lymphoma, ENKTL, and virus associated malignancies (Epstein-Barr virus (EBV) associated DLBCL and human herpes virus 8 (HHV8)-associated primary effusion lymphoma) (Table 2). Nodular lymphocyte-predominant HL, DLBCL-not otherwise specified, Burkitt lymphoma, and HHV8-associated Kaposi sarcoma did not express detectable PD-L1 [55]. In another study of 27 patients with DLBCL and 27 patients with FL, IHC results of biopsies showed that DLBCL tumors comprised a higher proportion of PD-1+, PD-L1+, PD-L2+, and LAG3+ lymphoma cells than the FL tumors, and the activated B cell (ABC) subtype comprised more PD-L1+ and PD-L2+ lymphoma cells than the GC subtype [56]. Other studies also reported that PD-L1 in tumor cells was rarely expressed in B-cell NHL, only confined to a subset of DLBCL (24–61.6% of primary DLBCL) with ABC and Non-GCB subytpes [57–59]. The prognostic role of PD-L1+ neoplastic cells in DLBCL is controversial. Some studies suggested there is no correlation between PD-L1 expression in neoplastic cells and OS [25,26]. In a large study of 273 patients with DLBCL, patients with PD-L1+ tumor cells had inferior OS compared with that in patients with PD-L1 − tumor cells. In addition, the expression of PD-L1 maintained its prognostic value for OS in multivariate analysis [60].

Zaja et al. evaluated the expression of PD-L1 in different nodal peripheral T-cell lymphoma (PTCL) subtypes and found that PD-L1 was expressed in 72% of anaplastic lymphoma kinase (ALK)+ and 46% ALK− ALCLs (with a 3–4 score in 11/16 and 5/8 cases, respectively). None of the neoplastic cells showed PD-L1 expression among AITLs (0/27) and PTCLs-NOS (0/73) [61]. Another study performed PD-L1 immunostaining in 135 ATLL biopsy samples and defined the patients with more than 50% PD-L1+ neoplastic cells as nPD-L1(+). Patients with nPD-L1(+) ATLL (median survival time 7.5 months) had inferior OS compared with those with nPD-L1(−) ATLL (median survival time 14.5 months), and the prognostic value was maintained in multivariate analysis [35]. A number of studies have examined the prognostic effects of PD-L1+ tumor cells in NK/T lymphoma and showed inconsistent results. In 79 patients with nasal NK/T-cell lymphoma (NNKTL), PD-L1+ tumor cells were observed in 79.7% of patients and these patients

Table 2
Clinical significance of PD-1/PD-L1 expression in neoplastic cells.

Biomarker	Author (Year)	Lymphoma (No. of patients)	Cutoff	Sample (Method)	Antibody (manufacturer)	Clinical significance
PD-1+ TC						
	Xerri et al. (2007) [44]	NHL (161)	–	Tissue (IHC) Peripheral blood (FCM)	–	PD-1 expression in neoplastic cells mainly associated with SLL in B-NHL; and was restricted to the angioimmunoblastic subtype in T-NHL.
	Grzywnowicz et al. (2012) [45]	CLL (58)	–	Peripheral blood (qRT-PCR and FCM)	eBiosciences	No correlation between surface expression of PD-1 in CLL cell with time to progression and OS, respectively.
	Cetinozman et al. (2012) [46]	Sézary Syndrome (27) Mycosis Fungoides (60)	positive: > 50%	Tissue (IHC)	AF1086	The expression of PD-1 in neoplastic T cells was different between SS (89% patients were positive) and MF/E-MF (13% patients were positive).
	Nguyen et al. (2017) [48]	CLD (42) SS (9) MF (103) CD30+ LPD (20)	positive: > 50%	Tissue (IHC)	Abcam	PD-1 seems to correlate with disease progression in epitheliotropic T cell dyscrasias ranging from minimal staining in (14.3%) to significant staining in MF (60.2%) and could used as a means of distinguishing CD30+ MF from primary cutaneous ALCL (CD30+ LPD did not show any PD-1 positivity).
	Park et al. (2014) [47]	CTCL (49)	positive: > 11%	Tissue (IHC)	Cell Marque	PD-1 was detected in 84.0% MF cases and in 45.8% other CTCL cases. No correlation was observed between disease course and PD-1 expression rate in the MF cases.
	Kurita et al. (2016) [49]	Lennert Lymphoma (26)	20%	Tissue (IHC)	NAT105 (Abcam)	Neoplastic cells positive for PD-1 were observed in 53.8% patients and was associated with poor OS.
	Muhamad et al. (2019) [32]	ENKTL (49)	positive: > 5%	Tissue (IHC)	NAT105 (Cell Marque)	PD-1 was undetectable on lymphoma cells in ENKTL.
	Jo et al. (2016) [33]	NNKTL (79)	NR	Tissue (IHC)	NAT105 (Cell Marque)	PD-1 in tumor cells was expressed at a very low level. (Neoplastic cells positive for PD-1 were observed in only 1.3% of patients).
	Zeng et al. (2019) [50]	ENKTL (88)	positive: > 5%	Tissue (IHC)	NAT	The expression level of PD-1 in TC was not associated with prognosis.
PD-L1+/PD-L2+ TC						
	Fang et al. (2017) [26]	DLBCL (76)	10%	Tissue (IHC)	SP142 (SGB-BIO)	PD-L1 positive expression in tumor cells showed low IPI score and worse OS in Kaplan–Meier analysis. But PD-L1 in tumor cells was not associated with OS by univariate analysis.
	Kwon et al. (2016) [25]	DLBCL (126)	NR	Tissue (IHC)	MRQ-22 (Cell Marque)	PD-L1 expression in TC was not associated significantly with patient prognosis.
	Kiyasu et al. (2015) [60]	DLBCL (273)	median	Tissue (IHC)	NAT105 (Abcam)	Patients with PD-L1+ DLBCL (PD-L1+ TC) had inferior OS compared with that in patients with PD-L1- DLBCL. There was no significant difference in OS between mPD-L1+ (PD-L1+ TIL) and mPD-L1- DLBCL.
	Laurent et al. (2015) [56]	DLBCL (27) FL (27)	–	Tissue (IHC)	PD-L1: SP142 (Fabien Soldevilla) PD-L2: AHP1704 (AbDSerotec)	DLBCL tumor cells comprised a higher proportion of PD-1+, PD-L1+, PD-L2+ and LAG3+ lymphoma cells than the FL tumor cells; and ABC subtype comprised more PD-L1+ and PD-L2+ lymphoma cells than the GCB subtype.
	ZAJA et al. (2016) [61]	PTCL (173)	positive: > 5%	Tissue (IHC)	NR	PD-L1 positive TC was expressed in 72% of ALK+ ALCLs and 46% ALK- ALCLs while no expression in AITLs and PTCLs-NOS.
	Miyoshi et al. (2016) [35]	ATLL (133)	nPD-L1(+): > 50% TC staining	Tissue (IHC)	ab174838 (Abcam)	nPD-L1(+) (PD-L1+ TC) ATLL had inferior OS compared with nPD-L1(-) ATLL.
	Jo et al. (2016) [33]	NNKTL (79)	NR	Tissue (IHC)	PD-1 (Cell Marque) PD-L1 (R&D Systems)	PD-L1-positive patients had a trend toward better OS compared with that in patients with PD-L1-negative in TC and TIL.
	Muhamad et al. (2019) [32]	ENKTL (49)	positive: > 5%	Tissue (IHC)	E1L3N (CST)	PD-L1 expression in tumor cells showed an unfavorable impact for OS and EFS.
	Zeng et al. (2019) [50]	ENKTL (88)	positive: > 5%	Tissue (IHC)	SP142	The expression level of PD-L1 in TC was an independently unfavorable factor in the prognosis of patients with ENKTL.

Abbreviations: PD-1, programmed death-1; PD-L1, programmed death ligand-1; TIL, tumor infiltrating lymphocyte; IHC, immunohistochemistry; OS, overall survival; DLBCL, diffuse large B cell lymphoma; NR, not report; PFS, progress-free survival; FC, flow cytometry; FL, follicular lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; NNKTL, nasal NK/T-cell lymphoma; TC, tumor cell; ATLL, adult T-cell leukemia/lymphoma; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic lymphoma; T-NHL, T-cell non-Hodgkin lymphoma; SS, Sézary syndrome; MF/E-MF, mycosis fungoides/erythrodermic mycosis fungoides; CLD, cutaneous lymphoid dyscrasias; LPD, lymphoproliferative diseases; CTCL, cutaneous t-cell lymphoma; PD-L2, programmed death ligand-2; IPI, international prognostic index; LAG3, lymphocyte activation gene 3; GCB, germinal center B cell-like; PTCL, peripheral T-cell lymphomas; ALCL, anaplastic large cell lymphoma; AITL, agio immunoblastic T cell lymphoma; PTCLs-NOS, pheripheral T-cell lymphomas not otherwise specipied.

seemed to have a better OS compared with that in patients with PD-L1-negative tumor cells [33]. However, in another study of 49 patients with ENKTL, the PD-L1 expression in tumor cells showed an unfavorable impact for OS and EFS [32]. Zeng et al. analyzed 88 ENKTL to screen out the prognostic markers to establish the molecular model for ENKTL prognosis [50]. They examined the expression of PD-1 and PD-L1 in tumor cells and found PD-L1 + tumor cells was an independent poor prognostic factor for OS with hazard ratio of 9.36.

7. Soluble PD-L1

A soluble form of PD-L1 (sPD-L1) was detected in the blood of patients with certain malignant diseases (Supplemental Table 1), which might be a potent predictive biomarker [62–65]. A number of investigators have reported that enzyme-linked immunosorbent assays (ELISAs) could detect sPD-L1 in serum [66,67] or plasma [63,68] of lymphoma patients. Despite differences in cutoff concentrations, these studies came to a consistent conclusion: Elevated sPD-L1 levels were associated with a poor OS or PFS in DLBCL [63,68], PTCL [69] and NKTL [66,67].

8. Chromosomal and genetic alterations

Recently, several studies have reported the genomic characterization related to PD-1 and PD-L1 expression in lymphoma (Table 3). In cHL, chromosome 9p24.1/CD274(PD-L1)/PDCD1LG2(PD-L2) alterations increase the abundance of PD-1 ligands, PD-L1 and PD-L2. The 9p24.1 amplicon also contains *JAK2* (encoding Janus kinase 2), and copy number-dependent JAK2 signal transducers. Activation of JAK2-signal transducer and activator of transcription (STAT) signaling further increases PD-1 ligand expression [70]. In a study analyzing 108 biopsy specimens from newly diagnosed cHL cases, alterations of the PD-L1 and PD-L2 loci (5% polysomy; 56% copy gain, 36% amplification) were identified in 97% of the cHL cases and were associated with PD-L1 protein expression. 9p24.1 amplification shortens PFS, and the incidence of 9p24.1 amplification was increased in patients with advanced cHL [71].

In non-Hodgkin lymphomas (NHLs), cytogenetic alterations affecting the 9p24.1 chromosome were observed in a subset of DLBCL cases [58,72,73], but more frequently in several specific types of large B-cell lymphomas, including primary mediastinal large B-cell lymphomas (PMBCL) [72,73], primary testicular lymphoma (PTL) [74], and primary central nervous system lymphoma (PCNSL) [74]. The *PDL2* gene was considered to best discriminate peripheral blood mononuclear cells (PMBCLs) from other DLBCLs [75]. Half of these rearranged *PDL1* and *PDL2* genes in PMBCLs were found to be fused to the class II, major histocompatibility complex, transactivator (*CIITA*) gene, leading to a decrease in MHC class II expression [76], which has been linked to poor OS [76] and disease specific survival (DSS) [77]. Structural variations (SVs) were reported in 27% of ATLL and 8% of DLBCL cases, which commonly disrupt the 3′ region of the *PDL1* gene and lead to a marked elevation of aberrant *PDL1* transcripts [78]. Patients with CLL were shown to have higher expression of PD-1 transcripts (*PDCD1*) from peripheral blood samples than healthy volunteers. Among these CLL cases, *PDCD1* expression was higher in patients with mutated *IGHV* genes (encoding immunoglobulin heavy chain variable regions) and had a strong inverse correlation with zeta chain of T cell receptor associated protein kinase 70 (ZAP-70) phosphorylation in the negative tyrosine residue 292, implying that PD-1 might modulate the function of ZAP-70 in CLL [79].

Table 3
Clinical significance of genomic characterization related to PD-1 and PD-L1 expression.

Biomarker	Author (Year)	Lymphoma (No. of patients)	Clinical significance
9p24.1 gains	Muenst et al. (2009) [19]	cHL (280)	The PD-1 + cell amount around neoplastic cells was lower in classical Hodgkin lymphoma cases with 9p24 gains.
CD274/PD-L1 PDCD1LG2/PD-L2,9p24.1 alteration	Roemer et al. (2016) [71]	cHL (108)	Alterations of the PD-L1 and PD-L2 loci (5% polysomy; 56% copy gain, 36% amplification) were shown in 97% cHL and were associated with PD-L1 protein expression. 9p24.1 amplification shortens PFS, and the incidence of 9p24.1 amplification was increased in patients with AS cHL.
PD-L1/PD-L2 locus	Georgiou et al. (2018) [58]	DLBCL (190)	Cytogenetic alterations include gains (12%), amplifications (3%), and translocations (4%) of the PD-L1/PD-L2 locus; and correlated with increased expression of PD-L1 but not of PD-L2. These alterations were more frequently observed in the non-GCB subtype.
3′-UTR disruption of PD-L1 gene	Kataoka et al. (2016) [78]	DLBCL (48) ATLL (12)	Structural variations commonly disrupt the 3′ region of the PD-L1 gene and lead to a marked elevation of aberrant PD-L1 transcripts, which were observed in 27% ATLL and 8% DLBCL.
IGHV gene mutation	Grzywnowicz et al. (2015) [79]	CLL (182)	The expression of PDCD1 (PD-1 transcript) was elevated in PBMC samples with mutated IGHV gene and showed strong inverse correlation with ZAP-70 phosphorylation.
9p24.1 rearrangement	Twa et al. (2014) [73]	PMBCL (125)	9p24.1 is rearranged at frequency of 20% break-apart and 29% amplification in PMBCL, more frequently as compared with DLBCL, FL and HL.
PDCD1LG2/PD-L2 gain	Shi et al. (2014) [72]	PMBCL (12) DLBCL (9)	PD-L2 protein is robustly expressed by the majority of PMBCLs (72%) but only rare DLBCLs (3%) and often associated with PDCD1LG2 copy gain.
MHC II	Roberts et al. (2006) [77]	PMBCL (42)	Poor patient survival in PMBCL correlated with incremental decreases in MHC II expression.
MHC class II transactivator CIITA	Steidl et al. (2011) [76]	PMBCL (77) HL (15)	Genomic CIITA breaks are highly recurrent in primary mediastinal B-cell lymphoma (38%) and cHL (15%). Presence of a CIITA rearrangement significantly correlated with a shorter disease-specific survival in PMBCL.
9p24.1/PD-L1/PD-L2 CNAs	Chapuy et al. (2016) [74]	PCNSL (49) PTL (43)	PCNSLs and PTLs have frequent 9p24.1/PD-L1/PD-L2 CNAs, which was linked with increased expression of the PD-L2. Additional translocations of these loci (CIITA et al) were also observed.

Abbreviations: PD-1, programmed death-1; PD-L1, programmed death ligand-1; HL, hodgkin lymphoma; OS, overall survival; DLBCL, diffuse large B cell lymphoma; PFS, progress-free survival; FL, follicular lymphoma; ATLL, adult T-cell leukemia/lymphoma; CLL, chronic lymphocytic leukemia; PD-L2, programmed death ligand-2; GCB, germinal center B cell-like; cHL, classical Hodgkin lymphoma; non-GCB, non-germinal center B cell-like; PBMC, peripheral blood mononuclear cell; IGHV, immunoglobulin heavy chain variable; ZAP-70, zeta-associated protein of 70 kDa; PMBCL, primary mediastinal large B-cell lymphoma; MHC, major histocompatibility complex; CIITA, class II transactivator; CAN, copy number alteration; PCNSL, primary central nervous system lymphoma; PTL, primary testicular lymphoma.

9. Conclusions

Previous clinical studies showed that PD-L1, but not PD-1, expression was associated with clinical response to PD-1 blockade and prognosis in solid tumors [13–16]. While in lymphoid malignancies, the expression patterns of PD-1 and PD-L1 are complex and variable in tumor cells or in the tumor microenvironment. Thus, it is necessary to evaluate the clinical role of PD-1 and PD-L1 expression in both immune cells and tumor cells, which evaluation might be valuable for predicting the response to PD-1 and PD-L1 blockade in lymphoid malignancies.

In the present study, we reviewed studies on PD-1 and PD-L1 expression and discussed various roles of PD-1-PD-L1 signaling in different lymphoma entities. In cHL, the frequency of 9p24.1 chromosomal alterations increases the abundance of PD-1 ligand expression. The incidence of 9p24.1 amplification is increased in patients with advanced cHL and shortens PFS. PD-1 + TILs, showing higher expression in lymphocyte-rich subtypes, seem to show trend toward poor survival when present in high amounts. In contrast to HL, PD1 + TILs in biopsy samples were found to be a favorable prognostic factor in DLBCL. While in blood samples, a higher percentage of PD-1 + CD4 + peripheral T cells was linked to significantly poor prognostic significance in DLBCL. PD-L1 expression in neoplastic cells was observed in a small subset of DLBCL, mainly associated with ABC subtypes and EBV positivity; however, the prognostic role of PD-L1 + neoplastic cells in DLBCL remains unclear. Higher numbers of PD1 + TILs were observed in FL than in other subtypes of B-cell NHL; however, their prognostic significance is controversial, suggesting a potentially complex role of PD1 + TILs in FL. A high degree of intrafollicular PD-L1 + macrophage infiltration was also observed in FL in a small-scale analysis and was shown to be associated with shorter time to transformation. Flow cytometry analysis of peripheral blood samples from patients with CLL showed that the expression of PD-1 in CD4 + or CD8 + T cells appeared to correlate with disease progression and poor prognosis, while PD-1 on the surface of tumor cells showed no significant prognostic value. In several specific types of large B-cell lymphomas, including PMBCL, PTL, and PNSL, the cytogenetic alterations affecting the 9p24.1 chromosome, including *CIITA* rearrangement, were more frequently observed and appear to have a potential role to worsen prognosis. With respect to T-cell NHL, PD-L1 expression in immune cells and tumor cells could be detected in ATLL and NNKTCL; however, the clinical significance related to prognosis is contradictory between these two subtypes. In studies focusing on the PD1 + neoplastic T cells in cutaneous T-cell lymphoma, including SS and MF, PD-1 seems to correlate with disease progression in epitheliotropic T cell lymphoma. In either T or B lymphoma, sPD-L1 showed consistent results: High levels correlated with poor response to treatment and survival. Our review demonstrates that the clinical roles of PD-1 and PD-L1 expressed in tumor cells and tumor-infiltrating immune cells are variable between multiple subtypes of lymphoma. Future studies will need to further delineate the prognostic and predictive role of PD-1 and PD-L1 expression, and explore the related mechanisms in depth.

Ethics committee approval and patient consent

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Authors contribution

MXX and XBH participated in writing the manuscript and drafting the table. XJY and WBQ reviewed and revised the manuscript. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105999.

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