Review Article

Responses and response evaluation of immune checkpoint inhibitors in lymphoma

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Abstract: The survival and growth of lymphoma cells relies on suppression of antitumor immunity through interactions between the tumor microenvironment and lymphoma cells. These are mediated by a network of inhibitory and stimulatory receptors that deliver signals as part of the maintenance of peripheral tolerance. The most studied pathway is the B7-1/B7-2:CD28/CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) pathway. Different molecules of this pathway are upregulated in lymphoma contributing to T-cell exhaustion and anergy and allowing tumor escape from the immune mechanisms. Additional activating and inhibitory signals modulate this pathway, and the inhibitory signal provided by the PD-L1/PD-L2:PD-1 (programmed cell death 1) axis has been found to be particularly important. PD-1 inhibitors promote immune activation and have recently been approved for the treatment of classical Hodgkin lymphoma (HL) that has relapsed after autologous stem-cell transplantation (SCT) and treatment with brentuximab vedotin. The clinical trials that led to their approval showed objective response (OR) rates over 70% and responses were durable. Less impressive responses have been described in non-HL due to the differences in the biology and composition of tumor microenvironment of these two types of lymphoma. Recently the response criteria were redesigned to reflect immune changes in the tumors caused by the medications used. Ongoing and future studies are focusing on the development of biomarkers for response assessment.

Keywords: Immune checkpoint inhibitors; lymphoma; response assessment

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Introduction

Immune checkpoints are inhibitory receptors which control the activation of T cells and thus play a critical role in the maintenance of peripheral tolerance and prevention of autoimmunity. The most studied pathway that is implicated in T cell activation is the B7-1/B7-2:CD28/CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) pathway. A network of stimulatory and inhibitory molecules interacts to deliver signals from the outside and maintain a balance between activation and inhibition. Programmed cell death 1 (PD-1) expression increases with cell activation leading to inhibition of further activation through interaction with its ligands and production of cytokines (1). Prolonged antigen stimulation in the setting of inadequate immune activation can result in upregulation of PD-1 and exhaustion of T cells.

Inhibitors of the PD-1 pathway have shown remarkable responses in clinical trials in several types of cancers including melanoma, non-small cell lung cancer and renal cell cancer. Nivolumab, a PD-1 inhibitor breakthrough therapy designation from the Food and Drug Administration (FDA) in 2014 for the treatment of relapsed or refractory classic Hodgkin lymphoma (HL) on the basis of a phase 1 trial which showed an 87% objective response (OR) in 23 heavily pretreated patients with HL, 78% of

whom had relapsed following previous autologous stem-cell transplantation (SCT) (2). Nivolumab subsequently received accelerated approval for this indication in May 2016. That was followed by accelerated approval by the FDA of pembrolizumab for a similar indication (patients with refractory classic HL whose disease relapsed after three or more lines of therapy) based on an OR rate of 73.9% seen in the KEYNOTE-087 trial (3).

In this review we will focus on the rationale for using immune checkpoint inhibitors in lymphoma, the spectrum of responses from PD-1 blockade in different types of lymphoma and the criteria that are used to assess response.

Rationale for targeting the PD-1 pathway in lymphoma

The activation of the T-cells is a two-step process. The first signal is a stimulatory signal that derives from the interaction of an antigen presented by the major histocompatibility complex (MHC) on an antigen presenting cell (APC) with the T-cell receptor (TCR) on a naïve T-cell. The second signal is a costimulatory signal that is generated when the CD3/CD28 molecule of the TCR binds to B7-1 and B7-2 on the APC (4). Lack of the co-stimulatory signals results in anergy (5,6). Following this initial interaction, stimulatory and inhibitory receptors on the surface of T-cells get involved and regulate this process. The inhibitory receptors, also known as immune checkpoint inhibitors, serve as breaks on the activation of the immune system in order to prevent autoimmunity and maintain peripheral tolerance (7-10). These include, amongst others, the CTLA-4 and PD-1 molecules, which are targets for cancer immunotherapy (11-15).

Pattern of expression of PD-1 and its ligands on immune and cancer cells

PD-1 is a transmembrane protein expressed on T cells, B cells and NK cells. Interaction of PD-1 with its ligands, PD-L1 and PD-L2, leads to recruitment of the protein tyrosine phosphatase SHP2 which dephosphorylates molecules transmitting signals from the TCR. This causes attenuation of TCR signal and increases T-cell exhaustion and conversion of effector T cells to Tregs (16-18). PD-L1 is constitutively expressed on B and T lymphocytes, dendritic cells, macrophages and mesenchymal stem cells, as well as many non-hematopoietic cells (19). It is also expressed on various cancer cells, including lung, breast (20), colon, skin, ovarian (21), gastric, pancreatic cancer, melanoma (21), as well as different types of hematologic cancers, such as chronic lymphocytic leukemia (CLL) (22), acute and chronic myelogenous leukemia (23,24), classic HL on Reed-Sternberg cells (25-27), primary mediastinal B-cell lymphoma (PMBCL) (27), Epstein-Barr virus (EBV)-positive and EBV-negative post-transplant lymphoproliferative disorder (PTLD) (26), EBV-associated diffuse large B-cell lymphoma (DLBCL) (28,29), follicular lymphoma (30), extranodal NK/T-cell lymphoma, HHV-8-associated Kaposi sarcoma and plasmablastic lymphoma (31). Although different cutoffs have been used to determine PD-L1 positivity in different studies, there is clear evidence that there is a correlation between the degree of PD-L1 expression and response to PD-1 inhibitors in solid tumors (32). Expression of PD-L1 on tumor cells is regulated at the level of transcription through epigenetic regulation via DNA methylation and histone modifications (33) and at the post-transcriptional level via alternative splicing (34). It can also be induced by IFN-gamma release by activated T-cells, a condition that is called "adaptive immune resistance" (35). In contrast, PD-L2 is expressed on active dendritic cells, macrophages and bone marrow derived mast cells (1,36,37). Expression of PD-L2 has also been identified in different tumor types, including both solid tumors, such as lung cancer (38) and hematologic malignancies, such as HL (39), PMBCL (40), primary CNS lymphoma and primary testicular lymphoma (41).

Significance of expression of PD-1 and its ligands in the pathogenesis of cancer

The expression of PD-L1 on cancer cells introduced the idea that PD-1 blockade might enhance antitumor immunity by suppressing the tumor ability to escape the immune effector mechanisms. That was confirmed by the observation that PD-L1 overexpression on a mastocytoma mouse inhibits CD8+ cytotoxic activity through PD-1 ligation and increases tumor growth and invasiveness (42). Different mechanisms are implicated in the evasion of the immune mechanisms by the tumors and promote tumor survival. Following PD-L1 ligation, anti-apoptotic signals are delivered to cancer cells inducing resistance against T-cell mediated cytotoxicity as well as apoptosis, which is normally induced by Fas and drugs such as staurosporine (43). On the contrary, delivery of apoptotic signals through IL-10 production and FasL expression, leads to death of antigen specific T-cells (21,44). In addition,

PD-1 ligation recruits the SHP-1 and SHP-2 phosphatases and impairs the activity of 2 pathways that are both critical for T-cell activation, the PI3K/Akt and Ras/MEK/Erk pathways. This is mediated via PTEN phosphorylation and inhibition of PLC-gamma (45-48). Finally, PD-1 ligation changes the metabolic program of T cells by switching from glycolysis, which is required for the function of effector cells, to fatty acid oxidation inducing conversion of effector cells to memory cells (49) and production of Tregs (17,50).

Significance of the PD-1 pathway in the pathogenesis of HL

As mentioned above, PD-L1 is highly expressed in lymphoma cells as well as infiltrating macrophages of both classic HL and non-HLs (NHL) (29). However, the biology of HL and NHL is significantly different. Classic HL are composed by a small number of malignant Reed-Sternberg cells within an extensive immune-cell infiltrate mainly composed by T cells (51). The exact composition of the tumor microenvironment determines the classification of the lymphoma to 1 of the 4 subtypes, which include nodular sclerosis, mixed cellularity, lymphocyte-depleted, and lymphocyte-rich HL (52) and depends on substances secreted by the Reed-Sternberg cells. The Reed-Sternberg cells have the ability to co-opt immune checkpoint pathways by expressing the PD-ligands on their surface. Such expression is mediated by the ERK/MAPK pathway (53). In preclinical studies, PD-1 blockade led to restoration of IFN-gamma production by T cells it the tumor microenvironment supporting the idea that PD-L1 expression on Reed-Sternberg cells suppresses the immune cell function in the tumor microenvironment (25).

Several mechanisms increase the expression of PD-L1. Amplification of chromosome 9p24.1 where the genes for the PD-ligands and JAK2 are located has been described in nodular sclerosis HL and has been associated with an increase in PD-L1 expression by immunohistochemistry (27). Analysis of biopsy samples from patients with both newly diagnosed and refractory or relapsed classic HL revealed copy gains of PD-ligand genes in almost all tested samples, ranging from low-level polysomy to uniform amplification (2,39). However, higher copy numbers are found in patients with advanced stage disease as opposed to early stage disease, a finding that suggests the role of PD-1 in tumor spread (39). Activation of the JAK/STAT pathway also increases transcription of the *PD-L1* gene and thus increases its expression further (27). Interestingly, 9p24.1 amplifications are associated with lower progression-free survival (PFS) in patients with new diagnosis of classic HL (39). Another mechanism that has been described to increase the expression of PD-L1 is *CIITA* gene fusion (54). In addition, in patients without 9p24.1 amplification constitutive activation of AP-1 transcription factor, which upregulates PD-L1 expression, has been described (26). Finally, EBV also activates the JAK/STAT pathway and increases PD-L1 expression (26). Of note, in a study that analyzed samples from both EBV-positive and EBV-negative classic HL, higher PD-L1 expression was detected in the EBV-positive tumors (39). Importantly, although almost all patients with nodular sclerosis have PD-L1 overexpression, only 13% of patients with lymphocyte predominant type express PD-L1 (29).

Role of tumor microenvironment in HL

In addition, the tumor microenvironment plays an important role in the survival and growth of lymphoma cells through T cell exhaustion (55) and upregulation of regulatory T cells (56). Indeed, T cells that are found in the tumor microenvironment and periphery of patients with HL express PD-1, although at low levels, which leads to anergy and T cell exhaustion (25,57) and PD-1 expression has been associated with poor prognosis (58). The characterization of the tumor microenvironment and its interactions with lymphoma cells remains an area of active research with some studies suggesting that it is mainly composed by activated and tumor specific TH1 rather than senescent TH2 cells (57). In addition, there is a high number of macrophages and monocytes which can further affect T cell activation by expression of PD-1 and delivery of inhibitory signals (29). Thus, the expression of PD-L1 on Reed-Sternberg cells and PD-1 on immune cells of the tumor microenvironment suggest the presence of an ineffective and suppressed T cell population in the tumor microenvironment and provides the rationale for targeting the PD-1 pathway in order to reactivate T cells and increase antitumor immunity.

Significance of the PD-1 pathway in the pathogenesis of NHL and CLL

In NHL, the PD-1 pathway also plays an important role in the signaling between the lymphoma cells and tumor microenvironment which affects the balance between antitumor immunity and tumor escape. The pattern of expression of molecules implicated in the PD-1 pathway

varies by type reflecting differences in the strategies used to escape the host's immune mechanisms. PD-L1 is expressed in various subtypes, including PBMC, EBV-positive and EBV-negative PTLD, EBV-associated DLBCL, extranodal NK/T cell lymphoma and nasopharyngeal carcinoma, dictating a more aggressive phenotype.

The majority of T-cell NHL and follicular lymphomas (FL) overexpress PD-L1 in the tumor microenvironment, which reflects suppression in host immunity (59). The tumor microenvironment of FL contains various T-cell subsets, including effector T cells, helper T cells and a high number of Tregs. Interestingly, the number of tumor infiltrating lymphocytes that express PD-1 decreases with transformation of FL to DLBCL and is a prognostic factor of overall survival (OS) (30).

In contrast, DLBCLs express both PD-1 and PD-L1 on the tumor cells and PD-L1 expression is associated more with the non-germinal B cell subtype (60). There is an association between PD-1 expression in tumor infiltrating lymphocytes and PD-L1 expression in tumor cells (61). In addition, DLBCL is characterized by recurrent cytogenetic abnormalities, including translocations of the locus for the PD-ligands with the locus of the immunoglobulin heavy chain (62). Soluble PD-L1 levels are associated with a poor OS are higher in patients diagnosed with DLBCL when measured at diagnosis and decrease back to normal levels in patients that achieve a complete response (CR) (63). Similar with HL, there is an association between gene amplification, viral infections and PD-L1 expression in NHL. PD-L1 expression is upregulated by EBV infection and chromosome 9p24.1 amplifications in non-germinal center DLBCL, primary CNS lymphomas and primary testicular lymphomas (41,64,65)

In CLL, T-cell exhaustion plays an important role in the pathogenesis of the disease and results in increased susceptibility to infections. PD-1 expression has been shown on both CLL and T cells and PD-1 blockade restored T-cell mediated cytotoxicity and prevented T cell exhaustion and progression of the disease in mouse models (66). PD-1 expressing T-cells of CLL patients are non-functional, they tend to be present in more advanced disease and their presence is associated with worse prognosis (67,68).

The aforementioned data regarding the significance of the PD-1 pathway and its ligands in the pathogenesis and progression of HL, NHL and CLL provide the rationale for PD-1 blockade in different trials in hematologic malignancies. These malignancies have been traditionally treated with combination of multiple chemotherapy agents and immunotherapies, such as rituximab. However, over the past few years several clinical trials have been testing the role of immune checkpoint inhibitors in these diseases with very promising results, which are reviewed below.

Spectrum of responses in lymphoma

PD-1 inhibitors in HL

HL, Hodgkin lymphoma; r/r, relapsed/refractory; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; FL, follicular lymphoma; CTCL, cutaneous T-cell lymphoma; SS, Sezary syndrome; MF, mycosis fungoides; CLL, chronic lymphocytic leukemia; RT, Richter's transformation; ORR, overall response rate; CR, complete response; OS, overall survival; PFS, progression-free survival; NR, not reached; SE, side effect; PR, partial response; SD, stable disease; PD, progressive disease; HSCT, hematopoietic stem-cell transplant; BV, brentuximab vedotin.

The response of different types of lymphoma to immune checkpoint inhibition varies due to the different mechanisms that are implicated in the expression of inhibitory receptors as well as the different composition of the tumor microenvironment. The clinical trials that have tested PD-1 inhibitors in lymphoma are summarized in *Table 1*. The best responses have been observed in refractory and relapsed classic HL, likely due to the extensive immune infiltrate that composes these tumors. HL is the first hematologic malignancy where PD-1 inhibitors were approved by the FDA. An OR was achieved in 87% of patients with HL treated with nivolumab that had relapsed following autologous SCT or brentuximab vedotin with an 86% PFS at 24 weeks. Only 17% of treated patients had a CR whereas a partial response (PR) was observed in 70% of treated patients. Further analysis of tumor samples revealed PD-L1 and PD-L2 copy-number gains in all patients tested (2). Follow up analysis at 101 weeks showed durability of responses with the median PFS not reached and a 1.5-year OS of 83% (76). This was followed by a phase II multicenter trial that included 80 patients with relapsed classic HL who had failed allogeneic SCT and had either failed or relapsed after brentuximab vedotin. At a median follow up of 8.9 months 66.3% of patients achieved an OR. The majority of responses were PR occurring in 57.5% of patients while only 8.8% of patients achieved a CR (69). Similar responses were seen in the KEYNOTE-087 trial that led to FDA approval of pembrolizumab. The OR

Table 1 Results from clinical trials on PD-1 inhibitors in lymphoma and CLL

Disease	Reference	Agent	Phase	Study population	Regimen	Results	SEs	Common SEs
HL	Ansell *et al.*, *NEJM* 2015 NCT01592370 (2)	Nivolumab	I	23 patients, r/r HL	3 mg/kg at w 1 and 4, then q2w for 2 years	ORR 87%, CR 22%, Median OS & PFS NR at 101 m, 1.5-year OS 83%	78% any SE; 22% ≥grade 3	Rash hypothyroidism diarrhea
HL	Younes *et al.*, *Lancet Oncol* 2016, NCT01592370 (69); Timmerman *et al.*, ASH 2016, NCT01592370 (70)	Nivolumab	II	Cohort 1, 6 m f/u: 80 patients, r/r HL, after HSCT & BV	3 mg/kg q2w	ORR 66.3%, CR 8.8%, PR 57.5%	90% any SE, 25% ≥ grade 3; 93% any SE, 29% ≥ grade 3	Hypothyroidism, rash, hypersensitivity
				Cohort 1, 12 m f/u: (same population)		ORR 67.5%, CR 8%, PR 60%		
				Cohort 2, 63 patients, r/r HL, after HSCT without BV		ORR 68%, CR 22%, PR 46%		
HL	Armand *et al.*, *JCO* 2016, NCT01953692 (71)	Pembrolizumab	Ib	31 patients, r/r HL	10 mg/kg q2w for 2 years	ORR 65%, CR 16%, PR 48%, 24w PFS 69%	97% any SE, 16% ≥ grade 3	Hypothyroidism, diarrhea, nausea, pneumonitis
HL	Chen *et al.*, *JCO* 2017, NCT02453594 (3)	Pembrolizumab	II	Cohort 1, 69 patients: r/r HL after HSCT & BV	200 q3w	ORR 73.9%, CR 21.7%, PR 52.2%	4% ≥ grade 3, 28.6% immune related SEs & infusion reactions	Hypothyroidism, pyrexia, diarrhea
				Cohort 2, 81 patients: r/r HL HSCT ineligible		ORR 64.2%, CR 24.7%, PR 39.5%		
				Cohort 3, 60 patients: r/r after HSCT without BV		ORR 70%, CR 20%, PR 50%		
DLBCL & PMBCL	Lesokhin *et al.*, *JCO* 2016, NCT01592370 (72)	Nivolumab	I	11 patients, r/r DLBCL, 2 patients, r/r PMBCL	Level 1: 1 mg/kg at w 1 and 4, then q2w for 2 years	DLBCL: CR 18%, PR 18%, SD 27%, median PFS 7w; PMBCL: SD 100%	71% any SE, 25% ≥ grade 3	Fatigue, pneumonitis, rash
					Level 2: 2–3 mg/kg at w 1 and 4; then q2w for 2 years			
PMBCL	Zinzani *et al.*, *Blood* 2017, NCT01953692 (73)	Pembrolizumab	II	18 patients, r/r PMBCL	10 mg/kg q2w or 200 mg q3w for 2 years	ORR 41.2%; CR 11.8%; PR 29.4%	61% any SE; 11% ≥ grade 3; 5.6% immune	Poor appetite, nausea, fatigue, hypothyroidism, diarrhea

Table 1 *(continued)*

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Disease	Reference	Agent	Phase	Study population	Regimen	Results	SEs	Common SEs
FL	Lesokhin *et al.*, *JCO* 2016, NCT01592370 (72)	Nivolumab	I	10 patients, r/r FL	Level 1: 1 g/kg at w 1 and 4; then q2w for 2y Level 2: 2–3 mg/kg at w 1 and 4; then q2w for 2 years	ORR 40%; CR 10%; PR 30%; Median PFS NR	72% any SE; 25% ≥grade 3	Fatigue, pneumonitis, rash
CTCL	Khodadoust *et al.*, *Blood* 2016, NCT02243579	Pembrolizumab	II	15 patients, r/r SS; 9 patients, r/r MF	2 mg/kg q3w for 2 years	ORR 38%; CR 4.2%; PR 33.3%	40% of SS skin flare reaction (2 grade 2, 4 grade 3)	Skin flare reaction
CLL	Ding *et al.*, *Blood* 2017, NCT02332980 (74)	Pembrolizumab	II	16 patients, r/r CLL; 9 patients RT	200 mg q3w	CLL: ORR 0%, SD 38.5%, PD 61.5%; RT: ORR 44%, CR 11%, PR 33%	100% any SE; 60% ≥ grade 3	Dyspnea, anemia
CLL	Jain *et al.*, *Blood* 2016, NCT02420912 (75)	Nivolumab & ibrutinib	II	5 patients, r/r CLL; 4 patients RT	3 mg/kg q2w	CLL: PR 60%; RT: PR 50%, PD 25%	1 immune related	Thyroiditis, tumor flare

HL, Hodgkin lymphoma; r/r, relapsed/refractory; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; FL, follicular lymphoma; CTCL, cutaneous T-cell lymphoma; SS, Sezary syndrome; MF, mycosis fungoides; CLL, chronic lymphocytic leukemia; RT, Richter's transformation; ORR, overall response rate; CR, complete response; OS, overall survival; PFS, progression-free survival; NR, not reached; SE, side effect; PR, partial response; SD, stable disease; PD, progressive disease; HSCT, hematopoietic stem-cell transplant; BV, brentuximab vedotin.

rate was 69% with 22.4% of patients achieving a CR and 39.8% a PR (3). Both studies included heavily pretreated patients that had relapsed following autologous SCT with most patients having received more than 3 previous lines of chemotherapy.

Despite the high response rates reported in HL the mechanisms via which HL responds to PD-1 blockade are not entirely known. Reed-Sternberg cells evade the host's immune mechanisms through loss of expression of MHC-I on their surface due to inactivating mutations in b-2-microglobulin. MHC-I expression on the surface of nucleated cells is responsible for antigen presentation to cytotoxic CD8 cells. Thus, loss of MHC-I expression leads to impaired recognition of cancer cells by T-cells decreasing antitumor immunity further. The b-2-microglobulin gene is amongst the most commonly mutated genes in classic HL, as demonstrated by full exome sequencing. Such mutations are more commonly found in the nodular sclerosis type defining a subtype of tumors with homogeneous molecular characteristics (77). Of note, EBV-negative classic HL expresses lower levels of b-2 microglobulin (78). Finally, lack of MHC expression on Reed-Sternberg cells is an independent negative prognostic factor in classic HL (79).

Side effects of PD-1 inhibitors in these trials were similar to the ones reported in solid tumors and overall the drugs were well tolerated. The most common side effects that occurred in up to 15% of patients in the nivolumab trial were fatigue, infusion reactions, rashes and thrombocytopenia. Immune side effects were reported in lower number of patients and included pneumonitis, colitis, hepatitis and hypophysitis (2,69,72). Treatment with steroids led to resolution of symptoms in most patients. Almost half of the patients developed grade 3 or greater adverse effects and the most common ones amongst them were neutropenia and pancreatitis, while others included myelodysplastic syndrome, pneumonitis, stomatitis, colitis and cytopenias (69). No treatment related deaths were reported and less than 10% of the patients had to discontinue treatment due to side effects. Toxicity was not increased over time when nivolumab was given for up to 2 years (2).

Of note severe graft-versus-host disease (GVHD) was reported in some patients who underwent allogeneic SCT after treatment with nivolumab and 6 transplant-related deaths were reported during the approval process of nivolumab by the FDA (80). Given the increased risk of severe GVHD associated with nivolumab treatment, this has been added as a warning to the drug label. Of note the initial nivolumab and pembrolizumab trial in HL excluded patients that had previously undergone allogeneic transplant because of the risk of worsening GVHD (2,3). In a recent case series, cytokine release syndrome at the time of transplant was reported in patients that received nivolumab followed by allogeneic SCT, although the mechanisms are not clear (81). In another retrospective cohort that analyzed 39 lymphoma patients who underwent allogeneic SCT at a median of 62 days after receiving PD-1 inhibitors, 44% developed grades 2–4 acute GVHD and 23% developed grades 3–4 acute GVHD. Four treatment related deaths were reported, 3 of which were due to acute GVHD. Given the 1-year PFS of 76% the authors concluded that allogeneic SCT is feasible after treatment with PD-1 inhibitors and leads to low relapse rates (82). With regards to the safety of administration of PD-1 inhibitors after allogeneic SCT, a recent study retrospectively analyzed the outcomes of 20 patients that received nivolumab for relapsed or refractory HL and had previously undergone allogeneic SCT, including 10 patients with previous acute GVHD. Reactivation of GVHD occurred in 30% of the patients and all of them had a history of acute GVHD. Two patients developed steroid refractory GVHD and 2 died of complications of GVHD. None of the patients experienced chronic GVHD. Overall response rate was excellent at 95% and median PFS was not reached (83). In summary, the use of PD-1 blockade either before or after allogeneic SCT is associated with good outcomes but also high rates of acute GVHD as well as severe GVHD.

PD-1 inhibitors in DLBCL

Responses to PD-1 inhibitors are less impressive in NHL due to the differences in biology of the two diseases and OR rates range between 15–50% in different subtypes of lymphoma. The reported OR rates with nivolumab in refractory or relapsed DLBCL were 36% in a phase I trial. Unfortunately, responses were not durable with a PFS of only 7 weeks 15% (72). These findings are supported by data that show overexpression of molecules involved in the B7-1/B7-2:CD28/CTLA-4 pathway (60). In addition, PD-L1 expression is a poor prognostic factor for OS in DLBCL (84). Consistent with the findings that EBV infection leads to overexpression of PD-L1, preclinical studies have shown that PD-1 inhibition is more potent in EBV-positive compared to EBV-negative DLBCL (64).

PD-1 inhibitors in FL

In FL OR rates of 40% have been reported (72). Similar to DLBCL, PD-1 overexpression has been described in FL (60). However, in contrast to DLBCL, the evidence regarding the prognostic significance of PD-1 and PD-L1 expression is controversial in FL (30,85), likely reflecting the variable T-cell subsets that comprise the tumor microenvironment (86).

PD-1 inhibitors in cutaneous T-cell lymphoma

In cutaneous T-cell lymphoma, PD-1 is expressed during early stages and levels of expression decrease when transformation occurs, while PD-L1 expression follows the opposite trend (87). The results of a multicenter phase 2 study of pembrolizumab in relapsed or refractory mycosis fungoides and Sezary syndrome were recently presented. Pembrolizumab led to OR rates of 38% in patients that had received a median of 4 prior regimens and most responses were PR. Responses were durable with 89% of them ongoing at a median follow up of 32 weeks. However, no correlations between PD-1 or PD-L1 expression and response to pembrolizumab were found. With regards to toxicity, 40% of patients with Sezary syndrome experienced a skin flare reaction (88). Durable responses have also been described in refractory or relapsed NK/T cell lymphoma that has failed asparaginase with CR persisting at 6 months of follow-up (89). That goes back to the biology of NK/T cell lymphomas which are EBV-positive and characterized by upregulation of PD-L1.

PD-1 inhibitors in mantle cell lymphoma

No responses have been noted in few patients with mantle cell lymphoma treated with either ipilimumab or nivolumab (72,90). Although only 4 patients with mantle cell lymphoma were included in the nivolumab trial which does not allow safe conclusions regarding the efficacy of nivolumab in this type of lymphoma, there are preclinical data showing the presence of a suppressed tumor immune environment in mantle cell lymphoma. Specifically, intratumoral Tregs found in the tumor microenvironment lead to inhibition of cytokine production of effector cells and PD-L1 expression on lymphoma cells decreases antitumor immunity through impairing T-cell proliferation and T-cell mediated cytotoxicity (56,91). These provide mechanisms for evasion of the host's immunity.

PD-1 inhibitors in CLL

A recently published study showed OR of 44% to pembrolizumab in heavily pretreated CLL patients with Richter transformation to DLBCL, that had progressed on ibrutinib, but no response in refractory CLL, despite promising preclinical data. The reasons for the different responses are not known but responses were durable with PFS of 5.4 months (74), in contrast to the short-lived responses in DLBCL where PFS was only 7 weeks.

Other checkpoint inhibitors and combination therapies in lymphoma

Other immune checkpoint inhibitors have also been tested in both HL and NHL. Ipilimumab, a CTLA-4 inhibitor, was first tested in 18 patients with relapsed or refractory B-cell NHL with only 2 patients achieving an OR. However, the role of the CTLA-4 pathway has not been elucidated in NHL. More recently, the combination of nivolumab with ipilimumab in refractory or relapsed hematologic malignancies was tested in a phase I trial the results of which were presented at the ASH 2016 meeting. Sixty-five heavily pretreated patients with HL, B-NHL, T-NHL, multiple myeloma (MM), and PMBCL were included in the study. Of note, only 13% of patients with HL had undergone previous autologous SCT. The overall response rate was 74% for HL, 20% in B-NHL, 9% in T-NHL, while none of the patients with MM responded. The researchers concluded that the combination of nivolumab with ipilimumab had similar efficacy and safety as nivolumab alone (92).

Ongoing trials are testing the combinations of agents that modulate expression of molecules of the PD-1 pathway with immune checkpoint inhibitors. Ibrutinib is a Bruton's tyrosine kinase inhibitor, an enzyme that plays an important role in the B-cell receptor pathway (93). It also has immunomodulating properties as it changes the balance between Th1 and Th2 by inhibiting ITK, another tyrosine kinase, which is important for the survival of Th2 cells, thus increasing antitumor immunity (94,95). Preclinical studies performed in mice with lymphoma and myeloma showed that the combination of PD-1 inhibitors and ibrutinib led to regression of tumors that were resistant to ibrutinib alone (95). Ibrutinib has shown to decrease both PD-1 and PD-L1 expression in samples from patients with CLL. Treatment with ibrutinib also decreases Tregs and improves cytotoxic CD8 activity as demonstrated by production of

IFN-gamma (96). Certain chemotherapy agents that are used in the treatment of lymphoma have also been shown to upregulate PD-L1 expression in the bone marrow stromal cells contributing further to immunosuppression and immune evasion by the tumor. Cytarabine and etoposide, amongst others, upregulate GM-CSF and activate the ERK pathway resulting in upregulation of PD-L1 which impairs T-cell function (97). Thus, immune checkpoint inhibitors could be used in combination with chemotherapy to eradicate the tumor cells that are able to evade the host's immune mechanisms through upregulation of PD-L1.

Assessment of response

Despite the durable OR in most trials, the majority of responses have a PR as opposed to a CR. In the nivolumab trial in HL, only 17% of patients had a CR, whereas the percentage of patients achieving a PR was 70%. Responses were durable with some patients continuing treatment for up to 2 years with acceptable toxicity (1). Similarly, in the KEYNOTE-087 trial 22.4% of patients achieved a CR while 46.7% achieved a PR. This cohort is currently being assessed for durability of responses and PFS at 24 weeks was 69%. It is important to point out that response was assessed with CT scans and PET-CT according to the Revised Response Criteria for Malignant Lymphomas in both studies (98). It is possible that in some cases the presence of stable disease, PR or a mixed response reflects the infiltration of the tumor by immune cells that are recruited with the use of immune checkpoint inhibitors rather than the persistence of malignant cells. The CR rate in these trials may therefore be higher than currently appreciated.

In the era of immune checkpoint inhibitors and other agents with immunomodulating properties it has been important to redesign the response criteria in order to reflect changes that may be explained by the immune effects of these medications. Immune checkpoint inhibitors have been associated with "pseudo-progression" on PET-CT due to increased recruitment of immune cells, despite clinical improvement (69,71). This consists of increase in the size of the already known lesions with delayed responses, appearance of new lesions in different areas while the known lesions are shrinking or increase in the FDG activity of the known lesions with stable size. Similar immune flares have been described with immunomodulating agents, like lenalidomide in both CLL and lymphoma and have been observed in up to 15% of patients within the first few weeks (99). These are attributed to NK-cell activation and increase in TNF-a levels causing an inflammatory reaction (100). Use of the old criteria for response assessment poses the risk of incorrect assumption that there is inadequate response to treatment leading to early discontinuation of a treatment that in fact beneficial.

Thus, immune response criteria were recently developed to assess response of both solid tumors and lymphoid malignancies to immune checkpoint inhibitors (101,102). In solid tumors, these require confirmation with subsequent imaging, measurement of the total tumor burden and assessment of durable disease (101). A recent study in melanoma patients receiving pembrolizumab showed that the implementation of the new immune criteria in solid tumors resulted in 15% decrease in the underestimation of patients (103). In lymphoid malignancies, the Lymphoma Research Foundation recently modified the Lugano criteria by introducing the LYRIC criteria (lymphoma response to immunomodulatory therapy criteria). In the LYRIC criteria, a new response category, indeterminate response, was added. Indeterminate response was defined as either an increase of the overall tumor burden occurring within the first 12 weeks of therapy, or the appearance of a new lesion without increase of the total tumor burden, or an increase in the FDG activity of the lesion without change in its size. These require confirmation of progressive disease (PD) on 2 consecutive scans 12 weeks apart (102). On the contrary, the RECIST and Lugano criteria define PD as the increase in tumor burden above a specified cutoff (20% and 50% respectively). It is important to point out that the Lugano criteria were designed to assess the response to conventional chemotherapy or combination of chemotherapy with rituximab. Importantly, clinical stability in the setting of indeterminate response is an important criterion for treatment continuation.

Thus, compared to conventional chemotherapy, responses with immune checkpoint inhibitors tend to be partial, often delayed and are more durable.

Finally, the early identification of patients that progress as opposed to having pseudo-progression is crucial. Towards that end, the use of minimal residual disease (MRD) and circulating DNA are being tested. Different techniques have been used for MRD assessment and include multicolor flow cytometry, end-point PCR, quantitative PCR and next generation sequencing. PCR can detect specific gene translocations in patients with common breakpoints, such as the translocation IGH-BCL2 in FL. Unfortunately, not all patients have a common translocation. On the other hand, circulating tumor DNA can be used in tumors without a

high number of circulating cells in the peripheral blood, such as DLBCL, as it relies on the detection of tumor specific DNA sequences that are found outside the cells (104,105). Despite the technical difficulties, improvement of these techniques can provide a better positive predictive value compared to PET scans which can be misinterpreted in patients treated with immune checkpoint inhibitors and have an inflammatory response manifesting either as pseudoprogression or as a PR. Mutational load and deficiency of DNA-repair genes could also serve as possible biomarkers. Soluble PD-L1 levels have also been reported to correlate with response as well as OS and could be further developed as a potential biomarker (74).

Summary

Immune checkpoint inhibitors have demonstrated promising results in both HL and NHL when used in heavily pretreated patients and results are more impressive in HL. Ongoing trials are testing drug combinations including PD-1 inhibitors for either salvage or first line treatment in both HL and NHL. As immune checkpoint inhibitors become more available, future research should focus on their combination with immunomodulating agents and chemotherapy agents with immunomodulating properties in order to increase the efficacy of these medications and optimize the treatment outcomes. This is supported by strong evidence stemming from preclinical studies and has the potential to change the outcomes of lymphoma patients in the future. The optimal duration of treatment also remains unclear and will be determined with longer follow up of patients undergoing treatment. Assessment of response also requires further research for the development of new biomarkers that will allow MRD detection and early identification of patients that progress. Finally, further preclinical research is required to dissect the mechanisms via which HL responds to PD-1 blockade.

In conclusion, based on their extremely promising results, PD-1 inhibitors have already been incorporated in the treatment of HL and ongoing studies are testing their role in earlier stages of the disease and specific subgroups of patients. At the same time, PD-1 inhibitors are an emerging treatment for several types of NHL and more trials are currently under way. Identification of the optimal timing for use of these drugs, optimal duration of treatment as well as use in combination with other agents in order to increase their efficacy will hopefully improve the outcomes of lymphoma patients in the future.

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Footnote

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