Chapter

Immune Checkpoint Inhibitors in Hodgkin Lymphoma and Non-Hodgkin Lymphoma

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Abstract

Lymphoma, which mainly includes Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL), is the most common hematological malignance of the lymphoid tissues with significantly heterogeneous characteristics. Tumor immune disequilibrium is involved in tumor development and progression, evading tumor immunosurveillance and suppressing anti-tumor immune responses. The tumor microenvironment (TME) is a complex network that comprises stromal cells and extracellular matrix, playing important roles in the pathogenesis, progression, and drug resistance of lymphoma. Therefore, a promising therapeutic strategy for lymphoma is by targeting the TME to stimulate anticancer immunity either by enhancing the release of immunostimulatory molecules or by mediating immune cell populations. Notably, immune checkpoint therapy (ICT) can provide durable clinical responses and improve overall survival in HL and NHL. However, different subsets of patients with lymphoma have different responses to ICT. Thus, significant challenges remain, including understanding pathways of resistance, optimizing patient selection, improving the management of immune-related adverse events, and identifying rational therapeutic combinations. This will allow a better understanding of the potential applications of ICT in lymphoma, guiding decisions to develop novel combination strategies with maximum efficacy and minimal toxicities for patients.

Keywords: tumor microenvironment (TME), immune checkpoint therapy (ICT), lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL)

1. Introduction

1.1 Biology of immune checkpoints inhibitors (ICIs)

T-cell activation is central to the immune response [1]. However, uncontrolled T cell activation leads to T cell exhaustion and autoimmune diseases [2, 3]. Therefore, it is crucial to maintain immune homeostasis and the balance of both co-stimulatory and co-inhibitory signals. These signals are thus referred as immune checkpoints. The major co-inhibitory receptors expressed on activated T cells are programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Here, we will briefly discuss their mechanisms of action.

1.1.1 Programmed cell death 1

PD-1 is mainly expressed on mature effector T cells within the peripheral and tumor microenvironment [4], responsible for immune tolerance. Besides T cells, PD-1 expression is also found on B cells, natural killer (NK) cells, dendritic cells (DCs), macrophages, and monocytes [5]. Therefore, it is an inhibitor of both innate and adaptive immunity. In cancers, numerous pathways are responsible for the upregulation of PD-1/PD-L1 signaling; and these major pathways include phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway, mitogen-activated protein kinase (MAPK) pathway, Jak-Stat pathway, Wnt pathway, NF-κB pathway, and Hedgehog (Hh) pathway [6]. Upon interaction with its ligands, programmed **cell death-ligand 1** or 2 (PD-L1 or PD-L2) expressed on cancer cells or antigen-presenting cells (APCs) of the tumor microenvironments [7–9], PD-1 signaling leads to T cell dysfunction, reduced cytokine production and anergy, thus protecting cancer cells from immune attack [10].

However, the detailed underlying mechanism of PD-1 signaling requires further elucidation. The inhibitory signal transduction of PD-1 needs both the interaction of PD-1/PD-L1 and peptide/MHC class I complex (MHC-I) from the same cells [11]. Src homology region 2 domain-containing phosphatase-2 (SHP-2) is a major downstream mediator of PD-1 and is capable of inhibiting key molecules and pathways such as ZAP70, PI3K/Akt pathway, and Ras pathway. Ultimately, PD-1 signaling counters the T-cell receptor (TCR) cascade and co-stimulatory receptor CD28 signaling in T cells, leading to reduced T cell activation and proliferation [11, 12]. Moreover, PD-1 can

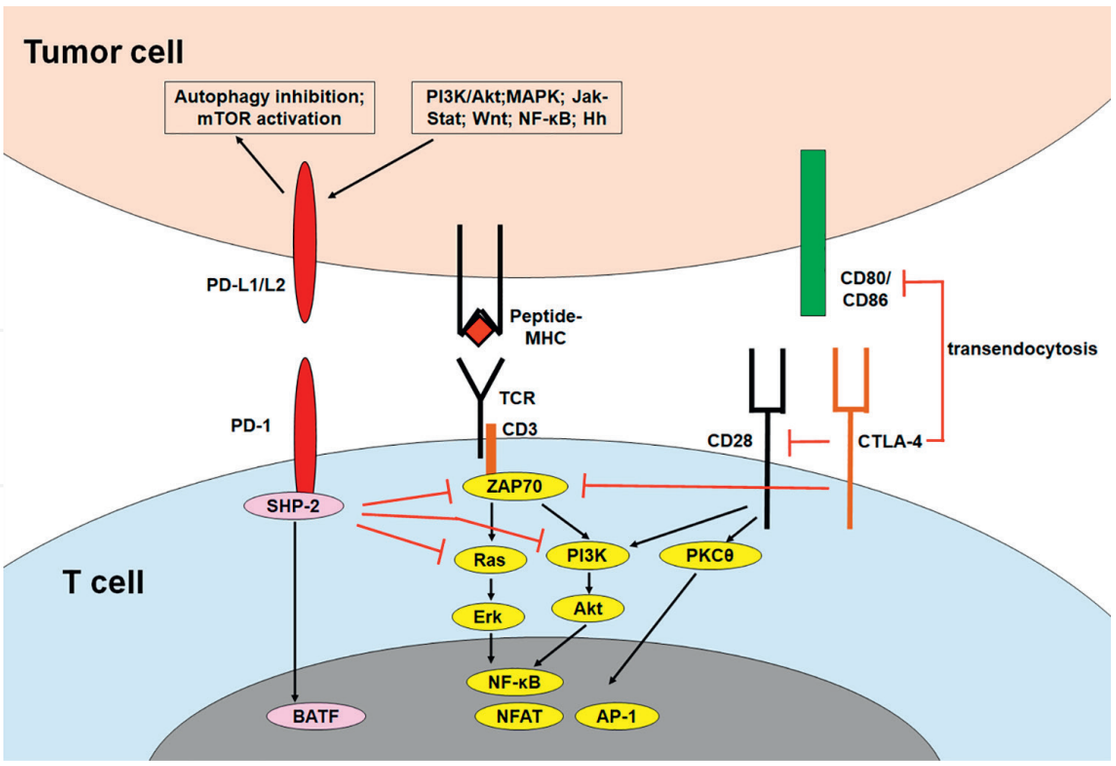

Figure 1.
Major immune checkpoints on T cells. PD-1 and CTLA-4 are the major co-inhibitory receptors expressed on activated T cells. Through ZAP70, PD-1 signaling is able to inhibit ZAP70, PI3K/Akt pathway, and Ras pathway, resulting in reduced T-cell activation. PD-1 can also directly induce T cell exhaustion by upregulating BATF. Furthermore, PD-L1 protects cancer cells in a PD-1-independent manner. CTLA-4 is a competitive inhibitor of co-stimulatory receptor CD28. It also inhibits T cell function via inhibition of ZAP70, PI3K/Akt pathway, cell-cycle progression, and trans-endocytosis of CD80/CD86.

directly exhaust T cells by upregulating the basic leucine transcription factor, ATF-like (BATF) [13]. Interestingly, PD-L1 may protect cancer cells in a PD-1 independent manner, leading to inhibition of autophagy and activation of mammalian target of rapamycin (mTOR; **Figure 1**) [14]. In addition, PD-1 is also highly expressed on regulatory T cells (Treg), enhancing its proliferation and immunosuppressive effects [12].

1.1.2 Cytotoxic T-lymphocyte-associated protein 4

In contrast to PD-1, CTLA-4 is mainly expressed in the endocytic vesicles of naïve T cells, and it translocates to the cell surface upon TCR activation. CTLA-4 shares the same ligands (CD80 and CD86) with co-stimulatory receptor CD28 (as competitive binding with higher affinity). Therefore, it can suppress T-cell activation [15, 16]. In addition, like PD-1, CTLA-4 is also able to directly inhibit ZAP70 to suppress TCR signaling and reverse T cell activation [17, 18]. Moreover, CTLA-4 exerts its immunosuppressive function via inhibition of PI3K/Akt pathway, cell-cycle progression, and removal of CD80/CD86 from the APCs via trans-endocytosis (**Figure 1**) [19–22]. Similar to PD-1, CTLA-4 is constitutively expressed in Tregs for immunosuppression and ligand (CD80/CD86) masking [4].

1.1.3 Blockade of immune checkpoints for cancer therapy

In cancers, the suppressive immune checkpoints introduced above are likely dysregulated, allowing them to escape from immune surveillance [23]. Therefore, blocking such immune checkpoints by antibodies is able to reverse the immune suppression for the treatment of cancers [24]. Preclinical studies have indicated that inhibition of immune checkpoints is able to enhance anti-tumor immunity. In the 1990s, initial research already indicated that the blockade of CTLA-4 by antibodies is able to reduce tumor burden in murine models [25, 26]. Since then, enormous advancements have been achieved in the use of immune checkpoint inhibition in cancer treatment, and the monoclonal antibodies targeting CTLA-4 and PD-1 have been approved by US Food and Drug Administration (FDA) for different cancers [27, 28]. In the following part of the chapter, we will summarize the current applications of immune checkpoint inhibitors (ICIs) for Hodgkin lymphomas (HLs) and non-Hodgkin lymphomas (NHLs).

2. Immune checkpoint inhibitors in Hodgkin lymphoma

2.1 Anti-PD-1 checkpoint inhibitors

In classical HL (cHL), malignant Reed-Sternberg cells harbor a recurrent chromosome 9p24.1 amplification. Such genetic abnormality encodes *PD-L1* and *PD-L2*, as well as *JAK2*, which further upregulates PD-1 ligand via the JAK-STAT pathway [29]. This upregulated PD-1 signaling allows cHL to suppress surrounding immune cells and survive from immune surveillance. Therefore, blocking PD-1 is likely to restore anti-tumor immunity and eradicate HL cells.

2.1.1 Nivolumab and pembrolizumab

Nivolumab and pembrolizumab are among the first fully human anti-PD-1 IgG4 monoclonal antibodies approved by the US FDA (May 2016 for nivolumab and March

2017 for pembrolizumab) for the treatment of relapsed or progressed cHL after autologous hematopoietic stem cell transplantation (auto-HSCT) and brentuximab vedotin (therefore referred as relapsed/refractory, r/r) [30, 31]. Since then, numerous clinical trials and real-world experiences have demonstrated the efficacy and safety profiles of nivolumab and pembrolizumab against HL, which is mainly (but not limited to) r/r cHL. Nivolumab and pembrolizumab are the most common ICIs used for r/r cHL patients, and many groups use both drugs in the same clinical trials (refers to them both as PD-1 ICIs). The clinical data of pembrolizumab are summarized in **Table 1** together with nivolumab.

As shown in **Table 1**, the objective response rate (ORR) for PD-1 ICIs is generally high (usually over 70%). However, the CR is rarely achieved, with a CR rate of around 30%–40%. Notably, some preconditions or previous treatments the patients experienced significantly enhance the outcomes of anti-PD-1 therapy. For example, 5 of 5 r/r cHL patients who have been given hypomethylating agents 5-azacitidine all achieved CR after ICI treatment [37]. This may suggest some potential combination therapies and numerous groups are assessing the efficacy of different treatment combinations.

2.1.1.1 Combination of PD-1 inhibitors and HSCT

The poor CR rate of anti-PD-1 antibodies suggests that monotherapy of PD-1 blockade alone may be not sufficient to cure r/r HL. Therefore, combined therapy of PD-1 blockade with other additional canonical treatments is necessary. It has been demonstrated that administration of PD-1 inhibitors before/after allogenic (allo-) or autologous (auto-) HSCT significantly enhances response rate and prolongs patient survival. Manson et al. [54] reported that none of the 13 r/r HL patients who underwent consolidation treatment of allo-HSCT together with nivolumab suffered from disease relapse. On contrary, 62.2% of those (n = 37) who did not undergo subsequent allo-HSCT relapsed. In another similar study, Merryman et al. [55] studied the 209 cHL patients who underwent subsequent allo-HSCT after PD-1 inhibition. With a median follow-up of 24 months, they reported that the 2-year progression-free survival (PFS) and overall survival (OS) were 69% and 82%, respectively. Merryman et al. also suggested that a shorter interval between PD-1 inhibition and allo-HSCT can significantly boost the graft-versus-lymphoma (GVL) effect of allo-HSCT. The real-life experience of 74 patients who underwent allo-HSCT after nivolumab treatment in Spain provided a similar conclusion (i.e., improved PFS and OS) as well [56].

Similarly, consolidation after auto-HSCT by PD-1 blockade also improves the treatment outcomes [57]. In this clinical trial (NCT02362997), the expected PFS after auto-HSCT increased from 60 to 82% upon pembrolizumab administration. Casadei et al. [58] also reported that auto-HSCT after PD-1 blockade further improved patient survival, with an estimated 5-year PFS of 73.4% and 4.8-year OS of 92.3%.

Although the combination of PD-1 inhibition and allo-HSCT seems to be a promising strategy against HL, increased graft-versus-host disease (GVHD) upon anti-PD-1 administration is a major concern of this treatment option [55, 56, 59]. Such GVHD can be severe and may cause multi-organ failure and even death [55, 56, 59–64]. Therefore, multiple studies indicated that post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis is required for improved PFS and therefore strongly suggested [55, 59].

Groups	Study status				Responses			Survival		AEs	
	Disease	Drug	Number	Follow-up	ORR	CR	PR	PFS	OS	Treatment-related AEs	>Grade 3
Liput et al. [32]	cHL	Nivo	10	NA	70%	60%	10%	—	—	80%	20%
Davis et al. [33]	r/r cHL (young patients)	Nivo	10	30 d	30%	10%	20%	—	—	Not reported for cHL separately	—
Kasamon et al. [34]	r/r cHL	Nivo	95	6 mo	65%	7%	58%	—	—	Lack overall summary	—
Bair et al. [35]	r/r cHL	Nivo, Pembro	53	13 mo	68%	45%	23%	12 mo: 75% Median: 29 mo	12 mo: 89%	Lack overall summary	—
Armand et al. [36]	r/r cHL after auto-HSCT	Nivo	243	18 mo	69%	16%	53%	Median: 14.7%	12 mo: 92%	Lack overall summary	—
Falchi et al. [37]	r/r cHL	Nivo, Pembro	9	9.9 mo	89%	78%	11%	—	—	100%	67%
Armand et al. [38]	r/r cHL	Pembro	31	17 mo	65%	16%	48%	24 wk.: 69% 52 wk.: 46%	24 wk.: 100%	97%	16%
Ansell et al. [39]	r/r cHL	Nivo	23	40 week	87%	17%	70%	24 wk.: 86%	—	78%	22%
Chen et al. [40]	r/r cHL	Pembro	210	27.6 mo	72%	28%	44%	Median: 13.7 mo	24 mo: 100%	73%	12%
Younes et al. [41]	r/r cHL	Nivo	80	8.9 mo	66%	9%	57%	6 mo: 76.9%	6 mo: 98.7%	99%	40%
Bekoz et al. [42, 43]	r/r cHL	Nivo	87	29 mo	70%	36%	34%	24 mo: 58.5%	24 mo: 78.7%	58%	12% of AEs
Geoerger et al. [44]	r/r HL pediatric patients	Pembro	15	8.6 mo	60%	13%	47%	Median: 12.2 mo 6 mo: 72.7% 12 mo: 51.9%	6 and 12 mo: 100%	Not reported for cHL separately	—
Maruyama et al. [45]	r/r cHL	Nivo	16	38.8 mo	87.5%	31.3%	56.3%	Median: 11.7 mo	3 yr.: 80.4%	100%	50%

Groups	Study status			Responses			Survival		AEs	
	Disease	Drug	Number	Follow-up	ORR	CR	PR	PFS	OS	Treatment-related AEs	>Grade 3
Ramchandren et al. [46]	untreated, advanced-stage cHL	Nivo	51	9.4 mo	84%	67%	17%	9 mo: 92%	—	96%	59%
Chan et al. [47]	r/r cHL	Pembro (low dose)	11	—	100%	73%	27%	Median: 35 mo	—	27.2	0%
Chan et al. [47]	r/r cHL	Nivo (low dose)	6	—	100%	67%	17%	Median: 33 mo	—	67%	0%
Dada et al. [48]	r/r cHL	Nivo	10	12.3 mo	80%	70%	10%	—	—	40%	0%
Kuruvilla et al. [49]	r/r cHL	Pembro	151	25.7 mo	65.6%	25%	41%	Median: 13.2 mo	—	75%	20%
Momotow et al. [50]	r/r HL	Nivo, Pembro	60	20.4 mo	65%	18%	47%	2 yr.: 42.3%	2 yr.: 78.4% 3 yr.: 65.8%	—	32%
Hur et al. [51]	Pretreated cHL	Nivo, Pembro	20	14 mo	75%	45%	30%	Median: 18 mo	Median: 36 mo	Lack overall summary	—
Lepik et al. [52]	r/r cHL	Nivo	99	21 mo	64%	31%	33%	Median: 19.4 mo	—	88%	17%
Armand et al. [53]	cHL after BV failure	Pembro	31	52.8 mo	58%	19%	39%	Median: 11.4 mo 24 mo: 30%	24 mo: 87% 36 mo: 81%	71%	19%

Numbers: number of patients; Follow-up: median or minimum follow-up; ORR: overall response rate; CR: complete response; PR: partial response; PFS: progression free survival; OS: overall survival; AEs: adverse events; r/r cHL: relapsed/refractory classical Hodgkin's lymphoma; d: days; mo: months; yr.: years; Nivo: nivolumab; Pembro: pembrolizumab; BV: brentuximab vedotin.

Table 1.
Overview of clinical efficiency and toxicity results of PD-1 inhibitors, nivolumab and pembrolizumab, in Hodgkin's lymphoma.

2.1.1.2 Other combined therapy

The regimen AVD regimen (doxorubicin, vinblastine, and dacarbazine) is the backbone of the well-established chemotherapy regimen ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for HL [65]. Therefore, the efficacy of nivolumab and AVD combination in early-stage cHL was assessed [66]. In total, 109 patients were given two different treatment strategies (of dosing and sequencing), and both groups displayed promising outcomes, with over 90% CR and nearly 100% 12-month PFS. Another multicenter, single-arm, phase II trial proved that pembrolizumab followed by AVD was both effective and safe in patients with untreated early unfavorable and advanced-stage cHL, with all patients (n = 30) achieving complete metabolic response (CMR) [67]. At the median follow-up of 22.5 months, the PFS and OS are 100%, indicating the superior efficacy of the strategy.

Brentuximab vedotin (BV) is a CD30-based antibody-drug conjugate. When used alone, it can lead to an ORR of 72% and CR rate of 33% in r/r HL patients [68]. Advani et al. [69] reported that BV combined with nivolumab can be the first salvage therapy in patients with r/r cHL, with an ORR of 85% and CR rate of 67%. In a median follow-up of 34.3 months, the estimated 3-year PFS and OS were 77% and 93%, respectively. Such combination treatment can be applied as a first-line option for older or chemotherapy-ineligible cHL patients, as demonstrated by Cheson et al. [70]. With a total of 46 patients and a median follow-up of 21.2 months, 48% of patients achieved CR and 13% achieved PR, with an ORR of 61%. Due to the high efficacy of this combination, it was considered as a salvage option after PD-1 blockade failure. In 21 r/r cHL patients who failed nivolumab monotherapy previously, BV combined with nivolumab resulted in an ORR of 57% [71]. Twenty-four-month PFS and OS were 31% and 80%, respectively. In total, 63% of patients suffered from adverse effects (AEs), but AEs of grade 3 or 4 were only observed in 10% of patients.

The potential synergistic effect of radiotherapy and ICIs has been proposed as well. In a cohort of 12 patients with r/r cHL, patients were given a combined treatment of radiotherapy and nivolumab/pembrolizumab, with an ORR of 100% and a CR rate of 58% [72]. With a median follow-up of 18 months, 92% of patients remained in CR (9 of 12 patients underwent HSCT consolidation). Forceville et al. [73] presented two case reports supporting that radiotherapy combined with nivolumab can lead to excellent outcomes.

Gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) are traditional second-line treatment options for r/r cHL, with a CR rate of around 50% [74]. In comparison, the combination of GVD and pembrolizumab resulted in an ORR of 100% and a CR rate of 95%, with a total of 39 enrolled r/r cHL patients [75]. In total, 36 of these 39 patients underwent subsequent auto-HSCT, and they all remained in CR at a median post-transplant follow-up of 13.5 months. In a similar trial consisting of 103 patients (27 for GVD + PD-1 blockade, 76 for GVD), the combination group had a higher CR rate of 85.2% (65.8% for the GVD group) and an extended PFS (1-year PFS of 82.2% vs. 67.9% for GVD group) [76].

2.1.2 Camrelizumab

Camrelizumab (SHR-1210), which was developed in China, is a humanized high-affinity anti-PD-1 IgG4 monoclonal antibody. It has shown promising efficacy against numerous advanced solid tumors including nasopharyngeal carcinoma, esophageal carcinoma, gastric and gastroesophageal junction cancer [77–81]. In a

single-arm, multicenter, phase II study (NCT03155425), a total of 75 patients with r/r cHL were given Camrelizumab 200 mg every 2 weeks intravenously. In a median follow-up of 12.9 months, 21 (28.0%) and 36 (48.0%) patients achieved complete or partial remission, respectively (i.e., objective response rate is 76.0%). Treatment-related adverse events (AE) were observed in all patients enrolled, with 20 (26.7%) of them exhibiting grade 3 or 4 treatment-related AEs [82]. The group further extended the follow-up of this clinical trial till 2020, with a median follow-up duration of 36.2 months. The objective response rate remained almost unchanged. The median PFS was 22.5 months and 3-year OS was 82.7%.

2.1.2.1 Combined therapy

Like other checkpoint inhibitors, although camrelizumab exhibits a high objective response rate in patients with r/r cHL, the CR rate remains low (as shown above). It has been proven that inhibition of *de novo* DNA methylation can boost T-cell function upon PD-1 blockade [83, 84]. Decitabine is a DNA demethylating agent [85]; therefore, clinical trial combining a low dose of decitabine with camrelizumab against r/r cHL was conducted (NCT02961101, NCT03250962). Indeed, when compared with camrelizumab monotherapy, r/r cHL patients receiving decitabine plus camrelizumab exhibited a higher CR rate (79% vs. 32%) and longer median PFS (35.0 vs. 15.5 months) [86, 87]. In addition, the administration of decitabine plus camrelizumab showed promising efficacy against HL with resistance to anti-PD-1 [86, 87]. Similarly, combination treatment of anti-angiogenic agent apatinib and camrelizumab might be a salvage option for r/r cHL patients who failed PD-1/PD-L1 inhibitor therapy, as demonstrated in the case reports presented by Yan et al. [88]. Out of seven enrolled patients, two achieved CR, and four achieved PR. The median PFS was 10 months, and no unexpected side effects were observed.

2.1.3 Sintilimab

Sintilimab is an anti-PD-1 antibody developed by Innovent Biologics, Suzhou, China. Shi et al. reported it exhibits comparable activity to nivolumab and pembrolizumab in patients with r/r cHL [89]. In their single-arm, multicenter, phase II trial (NCT03114683), 6-months PFS was 77.6%, and 74 of 92 fully analyzed patients (80.4%) achieved an objective response. Among those with objective responses, 31 (34%) had CR and 43 (47%) had PR. As for AE, 89 (93%) of 96 patients demonstrated treatment-related AE, including 17 (18%) with grade 3 or 4 and 11 (11%) with serious treatment-related AE (all expected).

2.1.4 Tislelizumab

Tislelizumab is a specially engineered humanized anti-PD-1 IgG4 monoclonal antibody. In contrast to other conventional PD-1 inhibitors, the Fcγ receptor (FcγR) fragment of tislelizumab was modified to minimize the binding of macrophages and the subsequent antibody-dependent phagocytosis. The antibody-dependent phagocytosis by macrophages could potentially lead to T-cell clearance and greatly affect the efficacy of anti-PD-1 therapy [90]. Therefore, the FcγR modification allows tislelizumab to exhibit improved anti-tumor function. In the single-arm, multicenter, phase II trial of tislelizumab in patients with r/r cHL (NCT03209973) [91], 61 of 70

(87.1%) patients achieved an objective response, including a high CR rate of 62.9% (44 of 70). The estimated median 9-month PFS was 74.5%. AEs were observed in 65 of 70 (92.9%) patients, with 15 (21.4%) experiencing grade 3 or 4 AEs.

2.1.4.1 Combined therapy.

Similar to other anti-PD-1 antibodies, co-administration of low-dose decitabine and tislelizumab for the treatment of r/r cHL has been reported. A 27-year-old male r/r cHL patient who failed eight lines of therapy (including PD-1 inhibition) achieved partial remission upon receiving decitabine plus tislelizumab treatment. No disease progression was observed during the entire 11.5 months of follow-up [92].

2.1.5 Zimberelimab

Zimberelimab (GLS-010) is the first fully human anti-PD-1 monoclonal antibody produced in a transgenic rat platform. While sharing the same heavy chain constant region as nivolumab and pembrolizumab, zimberelimab has two different modifications, namely S228P and N95S, in IgG4 core-hinge area and CDR3 area of the light chain, respectively. The S228P mutation prevents Fab-arm exchange, and the N95S mutation prevents the glycosylation of the antigen-binding domain [93]. Phase I studies for advanced solid tumors [94, 95] or preliminary studies for r/r cHL [96] have suggested high efficacy and acceptable safety. In a phase II trial for patients with r/r cHL (NCT03655483), 77 of 85 (90.6%) patients had objective responses, with a CR rate of 32.9% (28 patients). Twelve-month PFS and OS were 78% and 99%, respectively. Treatment-related AEs were found in 79 of 85 (92.9%) patients, with 24 (28.2%) of them demonstrated grade 3 or 4 and 1 exhibited grade 5 treatment-related AE (gastrointestinal infection) [93].

2.1.6 Penpulimab

Penpulimab is a humanized anti-PD-1 monoclonal antibody co-developed by Akeso Biopharma and Chia Tai Tianqing for the treatment of solid tumors. Similar to tislelizumab, the FcγR fragment region of penpulimab is engineered, through which the FcγR bindings of effectors (such as macrophages) are eliminated. As the results, T cells are protected from antibody-dependent cell-mediated cytotoxicity (ADCC), and the efficacy of tislelizumab is expected to be enhanced. In the open-label, multicenter, single-arm, phase I/II study (NCT03722147), the objective response rate was 89.4% (76 of 85 patients), with 40 (47.1%) patients achieving CR. Twelve-month PFS was 72.1%. Treatment-related AEs were observed in 97.9% (92 of 94) patients, with 25 (26.6%) experienced grade 3 or above treatment-related AEs [97, 98].

2.2 Anti-PD-L1 checkpoint inhibitors

Besides PD-1 blockade, targeting PD-L1 is an alternative strategy to avoid PD-1/PD-L1 immune checkpoints. However, it should be noted that PD-L1 and PD-L2, the two ligands to PD-1, are differentially expressed in the tumor microenvironment of cHL [29, 99]. Therefore, anti-PD-L1 monotherapy may be not sufficient to completely inhibit the PD-1 pathway, its efficacy may be lower than PD-1 inhibition alone. The use of PD-L1 inhibitors in HL should be carefully evaluated.

2.2.1 Avelumab

Avelumab (MSB0010718C) is a human anti-PD-L1 IgG1 monoclonal antibody. Besides blocking PD-1/PD-L1 interactions, the binding of avelumab on tumor cells induces ADCC via the FcγR binding [100, 101]. Unlike the ADCC induced by anti-PD-1 antibodies that impair T-cell function and dampen the efficacy of treatment, the ADCC induced by anti-PD-L1 antibodies provides another mechanism of tumor clearance and further enhances treatment efficacy. In a phase Ib trial of avelumab against r/r cHL [102], 13 of 31 (41.2%) patients showed an objective response, with six (19.4%) achieving CR and seven (22.6%) achieved PR. Twelve-month PFS was 18.2%, and the median PFS was 5.7 months. Treatment-related AEs were observed in 26 (86.7%) patients and 13 (43.3%) of them are grade 3 or 4.

2.2.2 Sugemalimab

Sugemalimab is a fully human, full-length, anti-PD-L1 IgG4 monoclonal antibody developed by CStone Pharmaceuticals for advanced solid tumors and lymphoma. In 2021, it has been approved in China for the first-line treatment of various forms of non-small-cell lung cancer in combination with different treatments. Phase Ia and Ib studies have been finished for sugemalimab against advanced malignancies (including 5 cHL patients in phase Ia study) [103]. They have demonstrated the safety and anti-tumor efficacy of sugemalimab. Currently, a single-arm, phase 2 trial of sugemalimab against r/r cHL (as monotherapy) is underway (NCT03505996) and has enrolled 80 patients [104].

2.2.3 Durvalumab

Durvalumab is another human anti-PD-L1 monoclonal antibody and has been approved by US FDA for urothelial carcinoma and stage III non-small-cell lung cancer [105]. Ogasawara et al. have conducted a pharmacokinetic analysis of durvalumab in 267 patients with hematological malignancies (including HL) [105]. They suggested the dosing regimen (1500 mg every 4 weeks) for hematologic malignancies can be the same as other solid tumors. This suggests a potential application of durvalumab against HL.

2.2.4 Atezolizumab

Atezolizumab is an inhibitor of PD-L1, and it has been approved by the US FDA and the European Medicines Agency for certain forms of solid tumors (such as triple-negative breast cancer or non-small-cell lung carcinoma, as monotherapy or used in combination) [106]. iMATRIX was a multicenter, open-label, phase I/II trial of young patients (<30 years old) with solid tumors or lymphomas (including nine HL patients, NCT02541604) [106]. Unfortunately, only two patients demonstrated objective response (PR). For the rest of the HL patients, two of them remained with stable disease, and five suffered from disease progression. Another phase II clinical trial of atezolizumab in r/r HL (NCT03120676) was also terminated due to lack of accrual.

2.3 Anti-CTLA-4 checkpoint inhibitors

2.3.1 Ipilimumab

In contrast to the wild application of anti-PD-1/PD-L1 inhibitor for the treatment of HL, very few studies have been conducted to assess the efficacy of anti-CTLA-4

inhibitor against HL. Ipilimumab is a fully humanized anti-CTLA-4 IgG1κ monoclonal antibody. Although several clinical trials of ipilimumab have been conducted for numerous solid tumors [107–110], and there are some ongoing clinical trials assessing the possibility of using ipilimumab in r/r cHL (like NCT04938232); currently very few reports have demonstrated the efficacy of ipilimumab as monotherapy in the treatment of HL. Bashey et al. reported that two out of 14 relapsed HL patients after allo-HSCT achieved CR upon ipilimumab treatment [111]. In comparison, the possibility of co-administrating ipilimumab with other agents against HL has been evaluated.

2.3.1.1 Combined therapy

In an open-label, multicenter, phase I trial assessing the efficacy of combination therapy in 61 patients with r/r HL (NCT01896999), patients were divided into three groups: combinations of brentuximab vedotin with ipilimumab (ipi-group) or nivolumab (nivo-group) or both (triplet-group) [112]. Although the overall response rates were similar for all three groups (76% for ipi-group, 89% for nivo-group, and 82% for triplet-group), triplet groups demonstrated a higher CR rate (73%), as compared with ipi- (57%) and nivo-groups (61%). These are also higher than the expected individual monotherapies. However, the inclusion of ipilimumab in the combination therapy significantly increased the chance of severe (grade 3 or 4) treatment-related AEs, with 43% in the ipi-group and 50% in the triplet-group. On contrary, this number is only 16% in the nivo-group. This may raise concerns for the possible higher toxicity of ipilimumab in treating Hodgkin lymphoma.

Lenalidomide is an FDA-approved drug for the treatment of multiple myeloma, with the ability of modulating cellular and humoral immunity and antiangiogenesis [113]. In a phase I dose-escalation study of ipilimumab and lenalidomide including seven refractory HL patients (NCT01750983) [114], PR was observed in one patient, and three patients experienced tumor shrinkage (less than PR).

2.4 Other potential immune checkpoint inhibitors

Besides the well-known immune checkpoints PD-1 and CTLA-4, novel immune checkpoints may be used as therapeutic targets for the treatment of HL. Halabi et al. found that lymphocyte-activation gene 3 (LAG-3) and T-cell immunoglobulin and mucin-domain containing 3 (TIM-3) are almost constitutively expressed in cHL [115]. Therefore, clinical trials targeting LAG-3 (relatlimab, NCT02061761) or TIM-3 (BMS-986258, NCT03446040) alone or in combination with nivolumab in the treatment of r/r HL are completed, and results will be released soon. In addition, T-cell Ig and ITIM domains (TIGIT) are another immune checkpoint receptor that is found to be highly co-expressed with PD-1 in r/r cHL patients [116]. Therefore, co-inhibition of PD-1 and TIGIT could be a novel strategy for treating r/r cHL.

Immune checkpoints are expressed in immune cells other than T cells, which could be targeted as well. In a phase Ib study, Armand et al. evaluated the efficacy and safety of dual inhibition of PD-1 and CTLA-4 (65 patients) or killer immunoglobulin-like receptors (KIRs) (72 patients) for r/r cHL [117]. KIR is expressed on NK cells and inhibits their function by interacting with MHC I [118]. However, the authors reported that the combination failed to further improve the efficacy, as compared with nivolumab monotherapy.

3. Immune checkpoints inhibitors in non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a mostly common and heterogeneous group of lymphomas derived from B and T lymphocytes, natural killer (NK), cells or precursors of these cells. Its pathology remains largely unexplained. Recent studies identified that tumor microenvironment (TME) in NHL is now playing a significant role in immune suppression and propagating tumor growth [119, 120]. Therefore, immunotherapies have been widely used and investigated in NHL to enhance or manipulate host anti-tumor immunity. In recent years, interference of PD-1/PD-L1 signaling, the immune checkpoint (therefore also known as checkpoint blockade), has been used in these kinds of lymphomas for its clinical efficacy by enhancing anti-tumor immune response. More importantly, therapeutic interference of checkpoint blockade has enjoyed significant success in cHL, but clinical response greatly varied in NHLs [121].

PD-1 and its ligands (PD-Ls), PD-L1 (also known as CD274 or B7-H1) and PD-L2 (as known as CD273 or B7-DC), form a signaling network that serves as a checkpoint to limit T-cell immunity, causing T-cell exhaustion [6, 122, 123]. Targeting PD-1 signaling to block T-cell activity with immune inhibitory antibodies can promote the activation, maturation, and proliferation of T-cells, eventually regulating anti-tumor activity, which has been investigated in NHL. Recent studies suggested that ICIs have been considered a promising and effective treatment strategy for some types of NHLs. Thus, PD-1 antibodies have been approved by the US FDA including nivolumab and pembrolizumab. Now, let us review the effectiveness of ICIs in NHL.

3.1 Immune checkpoints inhibitors in B-non-Hodgkin lymphoma

3.1.1 Diffuse large B-cell lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) represents 30–40% of all non-Hodgkin lymphomas (NHL) with a 60–70% curable rate in Rituximab Era [120]. However, about one-third of these patients are refractory or resistant to standard treatment. In addition, there are several subtypes of DLBCL in the 2016 World Health Organization (WHO) classification of lymphoid malignancies according to unique clinical and pathological features, including primary DLBCL of the central nervous system (PCNSL), primary cutaneous DLBCL, leg type, T-cell/histiocyte-rich large cell lymphoma, and EBV positive DLBCL of the elderly [124]. Nevertheless, most cases of DLBCL fall into the "not otherwise specified" (NOS) category [125]. As we know, immune evasion plays an important pathogenetic mechanism in DLBCL evolution, and immune checkpoint blockade therapy was explored in all kinds of lymphomas. But the outcome of immunotherapy remained controversial.

PD-L1 expression in DLBCL, with an incidence of ~25%, is associated with inferior outcomes, involving in DLBCL pathogenesis, which is considered a potential target [126, 127]. Importantly, chromosome 9p24.1 copy number alteration observed in DLBCL, in addition to cHL, is also involved in negative T cell regulation and NF-κb signaling pathway, which is associated with responsiveness to ICIs in relapsed/refractory DLBCL (r/r DLBCL) [126]. However, the results of ICIs in r/r DLBCL are disappointing [128, 129]. A phase I study to evaluate the safety and efficacy of nivolumab enrolled 81 r/r lymphoma patients (11 DLBCL) and showed an ORR of 36% in DLBCL. A recent phase II study (NCT02038933) showed that nivolumab monotherapy had good safety profiles but low ORR in DLBCL patients [130]. However, clinical trials of nivolumab combined with other immunochemotherapies are still in progress.

Pembrolizumab (Keytruda), a humanized anti-PD-1 MoAb with excellent anti-tumor activity, was explored in DLBCL. This study including 30 DLBCL patients, evaluated the efficacy of pembrolizumab (200 mg) with R-CHOP, and showed a 90% ORR, 77% CR, and 83% 2y-PFS at a median follow-up of 25.5 months, suggesting that this combination may be a promising treatment strategy [131]. All in all, the results of anti-PD-1 antibody in DLBCL patients are not promising in the current clinical trials, and anti-PD-1 antibody combination therapy is also under investigation [126].

It is a worthy note that anti-PD-L1 antibody atezolizumab (MPDL-3280A) combined chemotherapy seems a promising approach in DLBCL. In a phase I/II study, atezolizumab-R-CHOP for DLBCL demonstrated high efficacy (ORR of 87.5%) and durable responses (24 months for 80% of patients) for the combinational group [132]. Fifty-eight DLBCL patients enrolled in the study to assess the anti-tumor activity of atezolizumab associated with Venetolax (a BCL-2 inhibitor) and Obinutuzumab with 23.6% ORR (NCT03276468). In another phase 1/2 study, atezolizumab in combination with rituximab and polatuzumab in 21 participants with r/r DLBCL showed 57.14% ORR and 33.33% CR. In additional, atezolizumab with mosunetuzumab (a bispecific CD20-CD3 monoclonal antibody) was evaluated (NCT02500407). Certainly, anti-PD-L1 antibodies have been extensively investigated in combination with new-generation CD20 antibodies (NCT03533283), Chimeric antigen receptor (CAR)-T (NCT02926833), and ASCT (NCT02362997).

Durvalumab, another humanized IgG1-kappa monoclonal antibody against PD-L1, showed markedly anti-tumor activity in vivo. Thus, like atezolizumab, numbers of clinical trials are ongoing to investigate the value of durvalumab as a single agent or in combination with other treatment approaches or CAR T-cells in B-NHL patients. Encouraging results were commonly seen in patients treated with durvalumab in combination therapy in early studies. Durvalumab with Ibrutinib in DLBCL has 25% ORR and 4.6 months PFS [133]. Also, durvalumab combined with R-CHOP showed 54.10% CR but 51% serious AEs [134]. More interesting, remarkable results were found when combined with durvalumab and CAR T-cells in B-NHL including 12 DLBCLs, 2 high-grade B-cell lymphomas, and 1 PMBL (NCT03310619 (PLATFORM) and NCT02706405), which reported an ORR of 91%, including 64% CR [135, 136]. From these clinical results, AEs were frequently seen in combination therapy, which needed to be noted [137, 138].

Another inhibitor signaling of CTLA-4 including ipilimumab was not explored for its efficacy and safety. Recently, the combination of ipilimumab and nivolumab in patients with high-risk DLBCL after Allo-SCT has been opened (NCT02681302) [139]. More results should be worthy of expectation.

3.1.2 Primary mediastinal large B-cell lymphoma (PMBCL)

Importantly, anti-PD-1 MoAb has promising results in some special DLBCL. Primary mediastinal large B-cell lymphoma (PMBCL) comprises approximately 10% of DLBCL with different clinicopathologic and molecular signature, which have a good prognosis with R-CHOP/R-DAEPOCH combined with radiotherapy, with a 5-year event-free survival rate of 93% and OS rate of 97% [140]. However, more than 10% of patients still suffered relapsed or refractory, and the outcomes in r/r PMBCL remain poor. Studies have elucidated that PMBCL shared many similar biological features with cHL, including the importance of JAK-STAT and NF-κB signaling pathways as well as immune evasion [141]. Aberration expressions of PD-L1 and PD-L2 were found in PMBCL tumors, and the efficacy of anti-PD-1 antibody (pembrolizumab)

in r/r PMBCL was confirmed in phase 1 KEYNOTE-013 study [142]. Subsequently, a phase 2 study (KEYNOTE-170) has evaluated the efficacy of pembrolizumab in r/r PMBCL, and similar results were observed, with 45% ORR, and 13% CR, and median duration of response (DOR) not yet reached [143]. Thus, pembrolizumab has been approved in r/r PMBCL by FDA. After that, ICIs combined with other therapeutic agents for r/r PMBCL have been widely studied all over the world. Nivolumab combined with the anti-CD30 antibody-drug conjugate (ADC) brentuximab vedotin (BV) has been studied for r/r PMBCL in the CheckMate 436 study with an ORR was 73% and CR 37% [144]. These studies have identified the efficacy of PD-1 in PMBCL, especially combined with other agents. Numerous clinical trials assessing combination therapies with immune checkpoint inhibitors are ongoing [145].

3.1.3 Epstein-Barr virus (EBV)+ diffuse large B-cell lymphoma (DLBCL) and primary DLBCL of the central nervous system (PCNSL)

Epstein-Barr virus (EBV) is detected in a variety of B-cell lymphomas (BCLs) and lymphoproliferative disorders (B-LPD) with poor prognosis, associated with immunodeficiency, a key factor of lymphomagenesis. EBV+ DLBCL-NOS was first described as age-related EBV-associated LPD in 2003 with poor outcomes compared with EBV-negative DLBCL patients [146]. Unfortunately, the biology of EBV+ DLBCL-NOS remains unsure, and no standard approaches for these kinds of patients. Researchers have identified that 100% PD-L1 expression was seen in EBV+ DLBCL in a larger cohort study (n = 1100), which was significantly associated with EBV+ status [147, 148]. Liu et al. have identified that anti-PD-1 antibodies can restore and active function of T cells in EBV+ DLBCL [149]. Thus, the PD-L1/PD-1 pathway may be a potential therapeutic target for EBV+ DLBCL. Many studies are ongoing to assess the application of ICIs combined with chemotherapies in EBV+ DLBCL (e.g., NCT03212807, NCT04181489, NCT04705129, and so on).

Also, primary central nervous lymphoma (PCNSL) is a rare extra-nodal lymphoma with a high refractory/relapse rate using high-dose MTX-based treatment [150, 151]. For relapsed/refractory PCNSL (r/r PCNSL), new strategies have been explored including immunotherapy. PD-1 antibodies in r/r PCNSL have been reported with good efficacy in some case reports [152, 153]. Thus, some retrospective and prospective studies discussed the efficacy of anti-PD-1 antibody as monotherapy and in combination with other drugs [153, 154]. Unluckily, the results of ICIs in r/r PCNSL varied. Especially, we have seen promising efficacy in PCNSL with Bruton's Tyrosine Kinase and Immune Modulatory Small Molecules. Some explorations of ICIs in primary and r/r PCNSL are under study, especially for those who have higher PD-L1 expression and no chance to do MTX-based chemotherapy (NCT04899427, NCT05425654, and NCT04831658).

In other B-NHL entities, the rates of PD-L1 expression on neoplastic B cells are low: ~5% in FL, ~10% in high-grade MZL, and 0% in MCL. Therefore, slightly rare studies have been explored in these types of B-NHL.

3.2 Immune checkpoints inhibitors in T-non-Hodgkin lymphoma

PD-1 or PD-L1 has been used in various kinds of NHLs, either alone or in combination with other agents, which have promising results in some Lymphoma. For T-cell lymphomas, this strategy has been challenging because these markers may be expressed on the tumor cells themselves resulting in inadvertent tumor growth.

Peripheral T-cell lymphoma (PTCL) is a group of lymphoproliferative disorders, originating from mature T/NK cells with highly heterogeneous, aggressive characteristics and poor prognosis. There are 27 subtypes of PTCL in the World Health Organization 2016 classification of lymphoid neoplasm, including extranodal NK/T-cell lymphoma, nasal-type (ENKTL), nonspecific (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic lymphoma kinase (ALK)+/− anaplastic large cell lymphoma (ALCL) [155, 156]. CHOP-based regimens are the first-line treatments for PTCL other than NK/T-cell lymphoma, but the efficacy is limited [157, 158]. Thus, effective treatments for relapsed or refractory (r/r) PTCL are urgently needed. PD-1 and PD-L1 expression is commonly observed in PTCL cells, and PD-1 or PD-L1 is considered a prognostic biomarker and target. A phase I study (five patients with r/r PTCL) and phase 2 study (12 patients with r/r PTCL) have identified the clinical value of Nivolumab in r/r PTCL patients with 33% ORR [159, 160]. Also, the promising results using pembrolizumab have been seen in seven relapsed ENKT lymphoma with 100% overall response rates after a median of 7 weeks of treatment, either EBV DNA-positive or negative. The remission has been maintained at a median follow-up of 6 months. Similar results were reported for nivolumab. Thus, several studies are ongoing to explore the efficacy of PD-1 inhibitors in the treatment of ENKL. Studies showed that the response is correlated with the level of PD-1 expression, especially in EBV DNA positive patients. Although, studies were halted early due to the short duration of response and concern for hyperprogression. Encouraging results were also seen with pembrolizumab in patients with r/r cutaneous T-cell lymphoma with 38% ORR in a phase 2 study [142]. There was an alarming report of hyperprogression in three patients with ATLL that were enrolled in the nivolumab trial. Clinical progression was also accompanied by an increase in the viral load [143]. In these cases, PD-1 tumor suppressor function may have been lifted by PD-1 blockade. The use of PD-1 and PD-L1 antibodies in ATLL has to be viewed with caution. Therefore, more clinical trials should be done to evaluate the efficacy and safety of ICIs in different subtypes of PTCL.

Ipilimumab, an inhibitor of CTLA-4 (also known as CD152), provides both positive and negative feedback for T-cell activation when combined with its costimulatory receptor CD28. But the effect of CTLA-4 inhibitors in PTCL is not well characterized. In general, immunotherapy for PTCL is promising. For other immune checkpoint proteins, such as TIGIT, TIM-3, and LAG-3, their evaluation in PTCL is still at the preclinical stage and needed to be further explored via relevant clinical trials. Some studies have shown that the combined blockade of the TIM-3 and PD-1 pathways has significant efficacy in hematological tumors [161]. More importantly, the combination of PD-1/PD-L1 inhibitors and CAR-T cell therapy are worthy of exploring [162]. These ICIs combined therapies may be the best strategy for tumor therapy and promote the prognosis in near future.

4. Immune checkpoints inhibitors toxicity

As reported by the current clinical trials, treatment-related AEs were very common in patients undergoing anti-PD-1 treatment (**Table 1**). However, grade 3 or above treatment-related AEs were generally only observed in less than 30% of patients. Here, we use the studies with most patients enrolled as examples (i.e., n = 243 for Armand et al. [36] and n = 210 for Chen et al. [40]). As reported by Armand et al. [36], the most common treatment-related AEs of any grade were fatigue (23%),

diarrhea (15%), and infusion-related reactions (14%). However, none of them were severe (grade 3 or above). On contrary, the most common grade 3 or 4 treatment-related AEs were lipase increases (5%), neutropenia (3%), and ALT increases. The most common treatment-related AEs that led to treatment discontinuation were pneumonitis (2%) and autoimmune hepatitis (1%). Other serious treatment-relate AEs included infusion-related reactions (2%), pneumonia (1%), pleural effusion (1%), and pyrexia (1%). For the study conducted by Chen et al. [40], the most common treatment-related AEs were hypothyroidism (14.3%), pyrexia (11.4%), rash (11.0%), and fatigue (11.0%). The most common grade 3 or 4 treatment-relate AEs were neutropenia (2.4%) and diarrhea (1.4%). Fourteen patients discontinued treatment due to treatment-related AEs, and the most common causes were pneumonitis in seven (3.3%) and infusion-related reactions in two (1.0%). Here, we will briefly discuss some cases that deserve special attention.

4.1 Thyroid dysfunction

Thyroid dysfunction is one of the most common AEs observed during PD-1 inhibition and is heterogeneous in nature. In a study of 73 patients who underwent nivolumab therapy, Peiro et al. [163] reported that 23.3% of patients developed thyroid dysfunction. Among them, seven patients showed thyrotoxicosis and 10 patients showed primary hypothyroidism (four required levothyroxine treatment). They concluded that thyrotoxicosis occurred earlier than hypothyroidism. Before the onset of hypothyroidism, 33% of patients exhibited transient thyroiditis and five patients had hyperthyroid, which became hypothyroid later. In cases of thyroiditis, patients can be treated with beta-blockers, and thyroid hormone replacement may be required for hypothyroidism. For hyperthyroidism, beta-blockers and corticosteroids are very effective [164].

4.2 Treatment-related pneumonitis

In a meta-analysis of 11 clinical trials in patients treated with ICI (PD-1 or CTLA-4 blockade), the use of ICIs led to an increased risk of pneumonitis of all grades [165]. Younger age (<60 years old) may be a major risk factor [166]. Corticosteroids can be used for the treatment of pneumonitis, and those refractory cases should be treated with steroid-free immunosuppressants. For cases of grade 3 or above pneumonitis, potential infections should be considered. In cases of severe pneumonitis, the use of ICI should be stopped [167].

4.3 Treatment-related colitis/diarrhea

Gastrointestinal AEs are another most common treatment-related AEs during ICI therapy. Physicians should carefully distinguish colitis from diarrhea; and when colitis symptoms emerge, hospitalization and discontinuation of ICIs should be considered. In cases of mild symptoms, administration of corticosteroids or antidiarrheals could be applied [168], and additional infliximab may be needed [169].

4.4 Treatment-related cardiovascular disease

The incidences of treatment-related cardiovascular diseases are frequently underestimated, as reported by Jain et al. [170]. They identified 16,574 patients who received ICIs from a total of 2,687,301 patients and 1:1 matched to 2875 patients who received

chemotherapy or 4611 patients who received targeted agents. They observed the onsets of treatment-related cardiovascular diseases included stroke (4.6%), heart failure (3.5%), atrial fibrillation (2.1%), conduction disorders (1.5%), myocardial infarction (0.9%), myocarditis (0.05%), vasculitis (0.05%), and pericarditis (0.2%). In addition, anti-CTLA-4 therapy was more commonly related to treatment-related cardiovascular diseases. Moreover, another retrospective analysis indicated that inhibition of PD-1/PD-L1 was significantly associated with the risk of myocarditis, and males may have an increased risk of certain cardiovascular AEs [171]. In another meta-analysis including 2576 trials/studies and 20,244 patients, combined therapy of PD-1 blockade and chemotherapy may increase the risk of myocardial disease of all grades; although there was no significant increase in the risk of other cardiovascular diseases [172].

4.5 Other autoimmune diseases

As PD-1 blockade non-specifically activates the immune system, the induction of autoimmune-like diseases is the major concern of the toxicity incurred. Examples of symptoms during the treatment of HL include autoimmune type I diabetes [173–176], autoimmune encephalitis [177–179], autoimmune hepatitis [36], autoimmune nephritis [36, 38], and autoimmune hemolytic anemia [180, 181]. In cases of autoimmune diseases, the use of immunosuppressive treatment or delay of ICI therapy should be seriously considered.

4.6 Association between toxicity and efficacy

Although treatment-related AEs severely affect the treatment outcomes of ICIs, the onset of AEs that are immune-related may be directly associated with the efficacy of ICIs. In a study of 106 patients who underwent PD-1 blockade monotherapy, Rogado et al. [182] observed that patients with immune-related AEs have a higher ORR of 82.5% (vs 16.6%) and longer PFS of 10 months (vs 3 months), as compared with those without immune-related AEs. Although the detailed underlying mechanisms remain to be elucidated, concerns about the effect of corticosteroids and other immunosuppressants administration on ICI efficacy have been raised. However, some studies suggested that the use of corticosteroids and other immunosuppressants may not impair the anti-tumor activities of ICIs [183, 184].

5. Conclusions

ICIs therapies have demonstrated remarkable efficacy in several subtypes of HL and NHL, and some ICIs (e.g., pembrolizumab) have been approved to use in HL and PMBCL. Especially, anti-PD-1/PD-L1 antibodies in a combination with other therapies have acquired promising results, and AEs are common in these treatments. Thus, we need to do more clinical trials and real-world studies to further explore the effectiveness and safety of ICIs treatment in lymphoma.

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