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Immune checkpoint inhibitors and cellular treatment for lymphoma immunotherapy

F. Li,*[1] Y. Chen,*[1]
M. Pang, P. Yang and H. Jing
Department of Hematology, Lymphoma Research Center, Peking University Third Hospital, Beijing, China

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Correspondence: H. Jing, Department of Hematology, Peking University Third Hospital, 49 Huayuan North Road, Beijing 100191, China.
E-mail: hongmeijing@bjmu.edu.cn
*These authors contributed equally to this study.

Summary

Malignant lymphoma (ML) is a common hematological malignancy with many subtypes. Patients with ML usually undergo traditional treatment failure and become relapsed or refractory (R/R) cases. Recently, immunotherapy, such as immune checkpoint inhibitors (ICIs) and cellular treatment, has gradually emerged and used in clinical trials with encouraging achievements for ML treatment, which exerts anti-tumor activity by blocking the immune evasion of tumor cells and enhancing the attack ability of immune cells. Targets of immune checkpoints include programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and ITIM domain (TIGIT), T cell immunoglobulin-3 (TIM-3) and lymphocyte activation gene 3 (LAG-3). Examples of cellular treatment are chimeric antigen receptor (CAR) T cells, cytokine-induced killer (CIK) cells and natural killer (NK) cells. This review aimed to present the current progress and future prospects of immunotherapy in lymphoma, with the focus upon ICIs and cellular treatment.

Keywords: cell therapy, clinical trials, immune checkpoint inhibitors (ICIs), immunotherapy, lymphoma

Introduction

Malignant lymphoma (ML) is one of the most common hematological malignancies, accounting for 3–4% of all malignant tumors. It is a heterogeneous entity, generally divided into two main types as non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) [1–3]. Traditional treatments for lymphoma include chemotherapy, radiotherapy, surgery and bone marrow transplantation. On one hand, conventional chemotherapy and radiotherapy may lead to severe adverse events in low-risk lymphoma patients; on the other hand, some patients underwent disease recurrence after hematopoietic stem-cell transplantation in aggressive high-risk lymphoma patients [4,5]. Also, 30–40% of diffuse large B cell lymphoma (DLBCL) patients, which is the most common subtype of NHL, may relapse or become refractory (R/R) cases after standard treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) [6]. Thus, to find innovative and novel strategies to solve the current dilemma is an urgent matter.

In recent years, immunotherapy has gradually emerged and applied in clinical trials, with encouraging achievements for malignant lymphoma. The mechanisms of immunotherapy can be divided into two categories. One is to block the immune evasion of tumor cells, therapies represented by immune checkpoint inhibitors (ICIs) with the focus on programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and ITIM domain (TIGIT), T cell immunoglobulin-3 (TIM-3) and lymphocyte activation gene 3 (LAG-3) [7,8]. The other category is to enhance the attack ability of immune cells towards tumor cells, therapies represented by cellular treatment with chimeric antigen receptor (CAR)-T cells, cytokine-induced killer (CIK) cells and natural killer (NK) cells [9]. This review aimed to present the current progress and future prospects of immunotherapy in lymphoma (Fig. 1).

Immune checkpoint inhibitors (Table 1)

PD-1/PD-L1

As an immunosuppressive molecule, PD-1 is mainly expressed on activated T cells, B cells, NK cells and myeloid

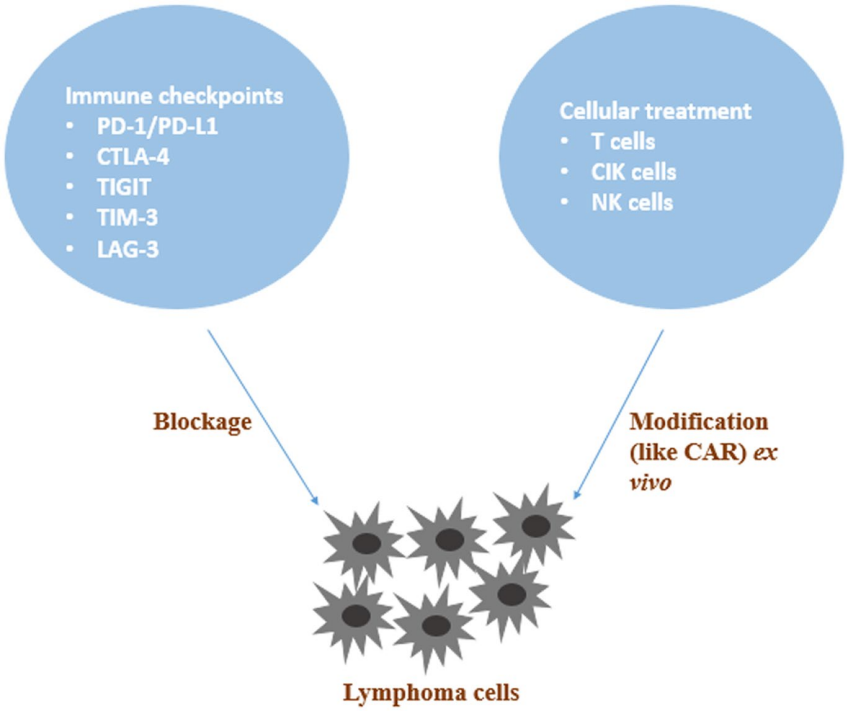

Fig. 1. Schematic diagram of lymphoma immunotherapy.

cells. In the tumor microenvironment, PD-1 on tumor-infiltrating T cells binds to PD-L1 on tumor cells, which suppresses T cell cytotoxicity. By blocking PD-1/PD-L1 signaling, the T cell-mediated immune response can be restored [10,11]. PD-1 inhibitors as nivolumab, pembrolizumab and pidilizumab and PD-1 inhibitors as atezolizumab, durvalumab and avelumab are exploited in clinical trials with various kinds of lymphoma patients.

Nivolumab (trade name: Opdivo), a fully human immunoglobulin (Ig)G4 anti-PD-1 monoclonal antibody, was first studied in 23 patients with R/R Hodgkin's lymphoma (HL) by Ansell *et al.* [12]. The results showed that the objective response rate (ORR) was achieved in 87% patients, with complete remission (CR) in 17% patients and partial remission (PR) in 70% patients. A Phase II clinical trial carried out by Younes *et al.* further confirmed the efficacy of nivolumab in 80 patients with R/R HL [13]. The ORR was 66.3%, with 9% patients obtaining CR, and the most common grades 3/4 adverse events (AEs) were neutropenia and increased lipase in 5% of patients. Another Phase I study conducted by Lesokhin *et al.* evaluated the efficacy of nivolumab in 10 patients with follicular lymphoma (FL), 11 patients with diffuse large B cell lymphoma (DLBCL) and five patients with peripheral T cell lymphoma (PTCL); the corresponding ORRs were 40, 36 and 40%, respectively [14]. Moreover, Nayak *et al.* observed the clinical outcome of nivolumab in four cases with R/R primary central nervous system lymphoma (PCNSL) and one case with recurrent primary testicular lymphoma (PTL) [15]. The results showed that four cases reached CR and one reached PR, with a median progression-free survival (PFS) of 9 months. Based on the encouraging results of nivolumab as a monotherapy, the clinical efficacy of nivolumab combined with other therapies were further explored. A Phase I/II clinical trial recruiting 61 patients with R/R HL assessed the tolerability and feasibility of nivolumab combined with brentuximab vedotin (BV) [16]. A total of 50 patients had objective responses and 60 patients underwent manageable AEs.

Pembrolizumab (trade name: Keytruda) is the second human IgG4 monoclonal antibody targeting PD-1. A Phase I clinical trial investigated the efficacy and safety of pembrolizumab in 31 classical HL (cHL) patients experiencing BV treatment failure [17]. Among these patients, ORR was 65%, with 48% patients developing PR; 16% patients had grade 3 AEs and no treatment-related deaths occurred. A subsequent Phase II clinical trial also explored the anti-tumor activity and safety profile of pembrolizumab in 210 subjects with R/R cHL, and the clinical outcomes were similar to the above Phase I study [18]. For R/R primary mediastinal large B cell lymphoma (PMBCL), seven of 17 patients responded to pembrolizumab and survived at the end of a Phase Ib study. Also, 11 patients suffered from treatment-related AEs and grades 1/2 AEs were mostly frequent [19]. For natural killer (NK)/T cell lymphoma, all the seven included subjects had responses to pembrolizumab and only one case underwent grade 2 AE [20].

Table 1. Clinical trials of immune checkpoint inhibitors (ICIs) in various types of lymphoma

Name of ICIs	Target	Clinical trial	Disease	Phase	Sample size	Efficacy	Safety	References
Nivolumab (Opdivo)	PD-1	NCT01592370	HL	I/II	23	4 patients (17%) had CR, 16 patients (70%) had PR and 3 patients (13%) had SD	18 patients (78%) had drug-related AEs, such as rash and a decreased platelet count	[12]
		NCT02181738	HL	II	80	7 patients (9%) had CR and 46 patients (58%) had PR	71 patients (89%) had drug-related AEs, such as fatigue, infusion-related reaction, rash, arthralgia, pyrexia, nausea, diarrhea and pruritus	[13]
		NCT01592370	NHL, MM	I	81	8 patients (8/31, 26%) had OR among B cell lymphoma; 4 patients (4/23, 17%) had OR among T cell lymphoma;1 patient (1/27, 4%) had OR among MM	53 patients (65%) had drug-related AEs, including non-hematological, hematological and immune-mediated AEs	[14]
		NCT02857426	PCNSL, PTL	II	5	All patients had OR; PFS in 5 patients was from 13+ months to 17+ months	Drug-related AEs occurred in one patient with grade 2 pruritus and another patient with grade 2 fatigue	[15]
		NCT02572167	HL	I/II	61	37 patients (61%) had CR, 13 patients (21%) had PR, 5 patients (8%) had SD and 4 patients (7%) had PD	60 patients (98%) underwent AEs, such as nausea, fatigue and infusion-related reactions	[16]
Pembrolizumab (Keytruda)	PD-1	NCT01953692	HL	I	31	5 patients (16%) had CR, 15 patients (48%) had PR, 7 patients (23%) had SD and 4 patients (13%) had PD; The rate of PFS at 24 weeks and 52 weeks was 69% and 46%, respectively	68% patients had treatment-related AEs, such as hypothyroidism, diarrhea, nausea and pneumonitis	[17]
		NCT02453594	HL	II	210	47 patients (22.4%) had CR, 98 patients (46.7%) had PR, 31 patients (14.8%) had SD, and 30 patients (14.3%) had PD	The most common treatment-related AEs were hypothyroidism (26/210, 12.4%) and pyrexia (22/210, 10.5%)	[18]
		NCT01953692	PMBCL	I	17	2 patients (11.8%) had CR, 5 patients (29.4%) had PR, 6 patients (35.3%) had SD and 3 patients (17.6%) had PD	11 patients (61%) had drug-related AEs, such as hypothyroidism, diarrhea, nausea, fatigue, pyrexia and decreased appetite	[19]
		NCT03021057	NK/T cell lymphoma	II	7	All patients had OR	1 patient had grade 2 rash	[20]
Pidilizumab (CT-011)	PD-1	–	AML, CLL, HL, NHL, MDS, MM	I	17	1 patient had CR, 4 patients had SD, and 1 patient had MR	11 patients (61%) had grade 1/2 AEs	[21]
		NCT00532259	DLBCL, PMBCL	II	72	12 patients had CR, 6 patients had PR, 13 patients had PD and 4 patients had PD	69 patients (96%) underwent 613 AEs, and the most common grade 3/4 AEs were neutropenia and thrombocytopenia	[22]
Atezolizumab (Tecentriq)	PD-L1	NCT02541604	Solid tumors, NHL, HL	I/II	90	4 patients had PR, 10 patients had PD and 63 patients had PD	57 patients (66%) had drug-related AEs, and the most common drug-related AE was fatigue (17 patients, 20%)	[23]
Durvalumab (Imfinzi)	PD-L1	NCT02401048	DLBCL, FL	Ib/II	61	15 patients (25%) had OR and the median PFS and OS was 4.6 months and 18.1 months, respectively	≥15% patients underwent treatment-related AEs and 34 patients (56%) had grade 3/4 treatment-related AEs	[24]

Table 1. (Continued)

Name of ICIs	Target	Clinical trial	Disease	Phase	Sample size	Efficacy	Safety	References
Ipilimumab (Yervoy)	CTLA-4	NCT00089076	B cell NHL	I	18	1 patient had PR for 19 months and 1 patient had 31+ months of PFS	No grade 4/5 AEs occurred and the most common treatment-related AEs were fatigue and diarrhea	[28]
		NCT01729806	NHL	I	33	2 patients had CR, 6 patients had SD, 11 patients had PD and the median PFS was 2.6 months	Toxicity was manageable, and the most common non-hematological AEs was diarrhea in 10 patients	[29]

OR = objective response; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; MR = minimal response; AEs = adverse events; PFS = progression-free survival; OS = overall survival; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; DLBCL = diffuse large B cell lymphoma; PMBCL = primary mediastinal B cell lymphoma; FL = follicular lymphoma; PCNSL = primary central nervous system lymphoma; PTL = primary testicular lymphoma.

Pidilizumab is a fully human IgG1 anti-PD-1 monoclonal antibody. A Phase I study was designed to estimate the toxicity and tolerability of pidilizumab in 17 patients with advanced hematological malignancies (including four patients with NHL). No drug-related toxicities were observed and AEs independent of the treatment appeared in 11 patients. Six patients responded to the treatment, including one case with CR. The half-life of pidilizumab in blood was approximately 9–17 days [21]. In another Phase II clinical trial, pidilizumab was evaluated in 66 patients with DLBCL after autologous hematopoietic stem-cell transplantation. The results suggested that the 16-month PFS in 24 high-risk patients (0·70, 90% CI = 0·51–0·82) was comparable to that in overall patients (0·72, 90% CI = 0·60–0·82); ORR was 51% among 35 evaluable patients [22].

Atezolizumab (trade name: Tecentriq) is a human IgG1 monoclonal antibody blocking PD-L1. A Phase I/II clinical study was executed to evaluate the safety profile and serum concentration of atezolizumab in children and young adults with R/R solid tumors, NHL and HL. Of the 90 enrolled patients, no mortal complications occurred and a high serum atezolizumab concentration was detected in all patients, while the efficacy was limited, with only four patients showing a response to the therapy [23]. Furthermore, some clinical trials are in progress to assess the anti-tumor activity of atezolizumab combined with other inhibitors or antibodies in DLBCL (NCT03276468, NCT02926833, NCT 02220842, NCT03321643, NCT03422523, NCT02596971) and FL (NCT03276468, NCT02631577, NCT02220842, NCT02596971). The efficacy of atezolizumab as monotherapy is also evaluated in DLBCL (NCT03463057), cutaneous T cell lymphoma (CTCL) (NCT03357224), PTCL (NCT03046953) and HL (NCT03120676).

Durvalumab (trade name: Imfinzi) is also a human IgG1 monoclonal antibody that inhibits PD-L1. In a Phase Ib/II clinical trial, the safety, tolerability and clinical response of ibrutinib plus durvalumab were measured in 27 cases with R/R FL and 34 cases with R/R DLBCL [16 germinal center B cell (GCB) subtype, 16 non-GCB subtype and two unclassified subtype]. Fifteen of 61 patients acquired an objective response (seven had CR and eight had PR), with a median response time of 11·3 months. Median progression-free survival (PFS) and overall survival (OS) were 4·6 and 18·1 months, respectively, and FL patients both had longer survivals than DLBCL patients. A total of 34 patients had grades 3/4 adverse events (AEs) and 12 patients had immune-related AEs, with no fatal AEs [24]. The safety and efficacy of durvalumab plus other drugs, radiotherapy or CAR-T cells are under investigation for lymphoma treatment, including DLBCL (NCT03003520, NCT03685344, NCT03610061, NCT 02706405, NCT03212807, NCT02549651), FL (NCT03685344, NCT03610061), mantle cell lymphoma (MCL) (NCT 03685344), NK/T cell lymphoma (NCT03054532), PTCL (NCT03161223, NCT03011814) and CTCL (NCT03011814).

Avelumab (trade name: Bavencio) is another human IgG1 monoclonal antibody targeting PD-L1, which has the ability to enhance antibody-dependent cell-mediated cytotoxicity [25]. Some clinical trials are designed to evaluate the feasibility of avelumab in DLBCL (NCT03244176, NCT 02951156, NCT03440567), FL (NCT03636503), MCL (NCT03440567), PTCL (NCT03046953, NCT03905135), anaplastic large cell lymphoma (ALCL) (NCT03905135), NK/T cell lymphoma (NCT03439501) and HL (NCT03617666, NCT02603419).

CTLA-4

CTLA-4 is a transmembrane receptor on T cells, which can induce T cell anergy and negatively regulate immune response when binding to B7 ligand on antigen-presenting cells (APCs) [26]. Blocking CTLA-4 causes increased T cell proliferation and activation to attack tumor cells.

Ipilimumab (trade name: Yervoy) was first introduced as the CTLA-4 inhibitor to treat metastatic melanoma patients [27]. The clinical efficacy of ipilimumab was studied in a Phase I clinical trial of 18 patients with R/R B cell malignant lymphoma. The study included nine cases of FL at grade 1, five cases of FL at 2 grade, three cases of DLBCL and one case of MCL. The results showed that one DLBCL achieved 31 months of continuous remission and one FL achieved 19 months of PR [28]. Another Phase I clinical trial performed by Tuscano *et al.* demonstrated the safety and efficacy of ipilimumab combined with rituximab in 33 patients with CD20-positive R/R B cell lymphoma. The clinical outcome indicated that eight patients (eight of 33, 24%) had a response with a median PFS of 2·6 months, while seven patients (seven of 13, 54%) had a response with a median PFS of 5·6 months, particularly in follicular lymphoma patients. Adverse events were under control and the ratio of $CD45RA^-$ regulatory T cells (T_{reg} : T_{reg}) could be associated with patient response using this therapeutic strategy [29].

Tremelimumab is another CTLA-4 inhibitor which was initially explored in malignant mesothelioma [30]. Three clinical trials are currently under investigation regarding the application of tremelimumab in lymphoma, including durvalumab combined with tremelimumab in R/R DLBCL (NCT02549651), MEDI6469 (OX40 monoclonal antibody) combined with tremelimumab in aggressive B cell lymphoma (NCT02205333) and tremelimumab combined with durvalumab and poly-ICLC [Toll-like receptor (TLR)-3 agonist] in cutaneous T cell lymphoma (NCT02643303).

TIGIT, TIM-3 and LAG-3

TTIGIT, TIM-3 and LAG-3 are newly discovered immune checkpoints that regulate immune function and are associated with cancer development. TIGIT is highly expressed in T_{regs}, follicular helper T cells, effector T cells and NK cells as a co-inhibitory factor mediating immunosuppression [31,32]. TIGIT was found in FL [33], various subtypes of NHL [34] and HL [35], indicating TIGIT blockage as a major concern of immune checkpoint therapies in the field of lymphoma. TIM-3 is a type of surface inhibitory molecule on $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells, which can cause T cell exhaustion during cancer progression and chronic virus infection [36,37]. In the context of lymphoma, TIM-3 demonstrated expression in DLBCL [38], NK/T cell lymphoma [39], PTCL [40] and FL [41], showing the potent anti-lymphoma activity of impeding TIM-3. LAG-3 is a negative immune regulator mainly distributed on activated T cells and NK cells [42]. LAG-3 expression was up-regulated in DLBCL [38], NK/T cell lymphoma [39] and FL [43], indicating that it might be the potential target for lymphoma treatment.

Cellular treatment (Table 2)

CAR-T cell therapy

CAR-T cell therapy is a novel adoptive immunotherapy by equipping T cells with 'CAR' to recognize specific tumor antigen. CAR consists of antigen-binding, transmembrane and signal transduction regions. T cells are extracted from peripheral blood and manufactured as CAR-T cells, which can enhance the anti-tumor activity of T cells for specific targets [44,45].

CAR-T cell therapy was first applied to attack CD19-positive B lineage malignancies due to CD19 expression on malignant and normal B cells [45]. Kochenderfer *et al.* reported the first case with FL who reached partial remission and maintained for 32 weeks after CD19-specific CAR-T cell therapy [46]. A Phase I/II multicenter clinical trial (NCT02348216) collected 108 patients with large B cell lymphoma who received a single dose of anti-CD19 CAR-T cellular treatment (axicabtagene ciloleucel) [47]. For efficacy evaluation, 84 of 101 evaluable patients had responses with a median duration of 11·1 months. For safety analysis, 52 of 108 evaluable patients suffered from at least grade 3 non-treatment-related AEs, including cytokine release syndrome (CRS) and neurotoxicity [47]. Subsequently, a Phase IIa single-center clinical trial (NCT02445248) recruited 93 patients with R/R DLBCL who were administered CD19-specific CAR-T cell infusion (tisagenlecleucel) [48]. Objective responses appeared in 52% patients and the rate of relapse-free survival was 65% within 1 year after response. Most patients underwent AEs-like cytopenias and CRS, with no treatment-related deaths [48]. Another CAR-T cell therapy (lisocabtagene maraleucel) with a distinct 1 : 1 $CD4^+$: $CD8^+$ ratio was investigated in 32 patients with R/R B cell NHL [49]. Twenty patients who had previously had lymphodepletion chemotherapy comprised of cyclophosphamide and

Table 2. Clinical trials of cellular treatment in various types of lymphoma

Cellular treatment	Target	Clinical trial	Disease	Phase	Sample size	Efficacy	Safety	References
CAR-T cells	CD19	NCT02348216	Large B cell lymphoma	I/II	108	59 patients had CR, 25 had PR, 10 had SD, and 5 had PD	All patients had manageable AEs and 106 had ≥ grade 3 AEs	[47]
		NCT02445248	DLBCL	II	93	37 patients (40%) had CR, 11 (12%) had PR, 14 (15%) had SD, and 24 (26%) had PD	111 AEs occurred, and 99 were related to treatment	[48]
		NCT01865617	$CD19^+$ B cell malignancies	I	32	19 patients had OR, with 10 achieving CR	4 patients had sCRS and 9 patients had ≥ grade 3 neurotoxicity	[49]
	CD20	NCT00012207	$CD20^+$ MCL or indolent NHL	–	7	2 patients had CR, 1 had PR and 4 had SD	No treatment-related AEs occurred	[50]
		NCT00621452	MCL, FL	–	4	2 patients had no evaluable disease and 1 achieved PR	Grades 1 or 2 AEs were most common and manageable	[51]
		NCT01735604	DLBCL		7	1 patient had CR for 14+ months and 3 had PR for 3–6 months	All patients had delayed treatment-related AEs, such as CRS, serous cavity effusion and lung dysfunction	[52]
	CD30	NCT02259556	$CD30^+$ R/R lymphoma	I	18	7 patients had PR and 7 had SD	All patients had grade 1/2 febrile syndrome, and nearly all the patients underwent cytopenias	[53]
		NCT01316146	$CD30^+$ R/R lymphoma	–	9	3 patients had CR and 3 had SD	No treatment-related AEs occurred	[54]
	CD19, CD70	–	PCNS-DLBCL	–	1	This patient achieved CR	Slight hematological toxicity was observed	[57]
CIK cells	–	–	HL, NHL	I	9	2 patients had PR and 2 had SD	Mild toxicities were observed and manageable	[62]
	–	–	HL, NHL	–	8	1 patients had CR and 7 had PR	All patients experienced fever and no serious complications happened	[63]
	–	–	HL,NHL, RCC, HCC	–	12	3 patients had CR and 2 had SD	2 patients had grade 2 fever	[64]
	–	–	Hematological malignancies	–	20	11 patients had CR, 7 had PR and 2 had SD	3 patients had mild malaise and low-grade fever	[65]
	–	–	DLBCL	–	9	All patients achieved CR	2 patients had mild fatigue and low-grade fever	[66]
NK cells	–	–	$CD20^+$ R/R NHL	–	6	2 patients had CR and 2 had PR	Non-hematological toxicities occurred, including rigors and fevers, skin redness/swelling, fatigue, etc.	[73]
		NCT01181258	R/R NHL and CLL	–	16	2 patients had CR, 2 had PR and 10 had PD	All patients underwent hematological toxicities, including thrombocytopenia, anemia and neutropenia	[74]
NK-92 cells	–	NCT00990717	HL, NHL, MM	I	12	2 patients had CR, 2 had MR and 7 had PD	Acute toxicities included fever and/or chills, blurred vision, nausea and pneumonia	[75]
CAR-NK cells	CD19	NCT03056339	$CD19^+$ NHL and CLL	I/II	11	8 patients had OR, including 7 with CR	None had CRS, neurotoxicity or GVHD	[83]

CAR-T cells = chimeric antigen receptor T cells; CIK cells = cytokine-induced killer cells; NK cells = natural killer cells; OR = objective response; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; MR = minor response; AEs = adverse events; CRS = cytokine release syndrome; sCRS = severe CRS; HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; MCL = mantle cell lymphoma; FL = follicular lymphoma; R/R = refractory or relapsed; PCNS-DLBCL = primary central nervous system diffuse large B cell lymphoma; RCC = renal cell carcinoma; HCC = hepatocellular carcinoma; CLL = chronic lymphocytic leukemia; MM = multiple myeloma; GVHD = graft-*versus*-host disease.

fludarabine (Flu) achieved 72% ORR and 50% CR, with stable CAR-T cell expansion and persistence *in vivo*. CRS and neurotoxicity were observed in 13 and 28% of all 32 patients [49].

Studies regarding anti-CD20 CAR-T cell therapy were also explored. Till *et al*. reported seven cases with R/R FL successfully infused anti-CD20 CAR-T cells for treatment (NCT00012207), and demonstrated the safety and effectiveness in these patients [50]. They subsequently used anti-CD20 CAR-T cells with co-stimulatory domains of CD28 and 4-1BB to treat three MCL and one FL (NCT00621452), and again proved the feasibility and tolerability of this method [51]. Another study assessed the anti-tumor activity of CD20-specific CAR-T cells in seven patients with advanced DLBCL; these patients achieved at least 3 months of tumor regression. AEs were considered to be associated with tumor size and location [52].

CAR-T cell therapy targeting CD30 may provide alternatives for patients with CD30 positive R/R HL or NHL. In a Phase I clinical trial, anti-CD30 CAR-T cell therapy was applied in 18 patients with R/R HL [53]. The results showed that seven patients had PR, two patients appeared to be grade ≥ 3 AEs, serum CAR-T cells increased and CD30 antigens decreased, proving that anti-CD30 CAR-T cell therapy was tolerated and effective. Another Phase I study regarding CD30-specific CAR-T cell therapy was performed in seven cases with R/R HL and two cases with R/R ALCL [54]. The clinical outcome showed that three patients achieved CR with a response duration of 9 months, 2 years and > 2·5 years, respectively. Serum CAR-T cells persisted for more than 6 weeks, and no treatment-related toxicities occurred.

Dual-target CAR-T cell therapy, which means that CAR-T cells are manufactured to recognize bispecific antigens, has become a new focus in lymphoma immunotherapy. Preclinical data illustrated the anti-tumor activity of anti-CD19$^-$CD20 CAR-T cells towards B cell malignancies [55,56]. Tu *et al*. discussed a case presented with R/R PCNS-DLBCL using CAR-T cells against CD19 and CD70 [57]. The patient achieved CR within 1 month and disease-free survival for more than 17 months; no neurotoxicities occurred. Additionally, CD19/CD22 bispecific CAR-T cell therapy was investigated in patients with acute B cell lymphoblastic leukemia and considered to be safe and efficient [58].

CIK cell therapy

CIK cells originate from peripheral blood mononuclear cells with stimulation of interferon (IFN)-γ, interleukin (IL)-2 and anti-CD3 monoclonal antibody [59]. CIK cells express both CD3 and CD56 markers, with strong anti-tumor activity-like T lymphocytes and non-major histocompatibility complex (MHC)-restricted tumor killing-like NK cells [60,61].

A Phase I clinical trial conducted by Leemhuis *et al*. explored the efficacy of CIK cellular treatment with different doses for relapsed B cell lymphoma after autologous transplantation. Two patients achieved partial response and two patients achieved stable disease among the nine enrolled patients, while no relationship was found between dose level and clinical outcome due to the small sample size [62]. Guo *et al*. also performed a retrospective study to demonstrate the feasibility of CIK treatment in eight patients with refractory lymphoma after various chemotherapy regimens. All these patients had complete response or partial response with no serious complications after CIK cell infusion, indicating the effectiveness and safety of this novel therapy [63]. Another study proved that CIK cellular treatment could improve immunity in refractory or relapsed lymphoma patients, with increased level of $CD3^+CD8^+$ and $CD3^+CD56^+$ cells in their peripheral blood [64–66]. CIK cell therapy was also safe and effective for elderly patients with malignant lymphoma [65,66].

NK cell therapy

NK cells are important innate immune cells, which can kill tumor cells without antigen pre-sensitization [67,68]. NK cells can exert cytotoxicity through a series interaction of activated and inhibitory receptors and corresponding ligands. The most common mechanism is called 'missing-self', meaning that low expression of human leukocyte antigen (HLA)-I molecules on the tumor cell surface leads to the escape of tumor killing by cytotoxic T cells but activates tumor killing by NK cells [69]. Activated NK cells directly kill target cells by releasing perforin and granzymes [70]. Another important way technique for activating NK cell function is mediated by IgG, termed 'antibody-dependent cell-mediated cytotoxicity' (ADCC). Here, the Fab segment of IgG links to the antigen epitopes of tumor cells while the Fc segment of IgG links to CD16 expressed on NK cell surface; target cells are then directly killed by NK cells [71,72].

In 2010, Bachanova *et al*. first investigated the clinical efficacy of adoptive haploidentical donor NK cells combined with IL-2 and rituximab to treat six relapsed or refractory $CD20^+$ NHL patients [73]. The addition of IL-2 and rituximab enhanced the NK cell-related ADCC effect. Four of six patients obtained complete response (two cases) and partial response (two cases), while NK cell survival was transient (no more than 7 days) in these patients with increased levels of T_{regs}. Another study was also performed by Bachanova *et al*. in 2018 [74], and four of 14 patients obtained complete response (two cases) and partial response (two cases). In this study, NK cells persisted *in vivo* for at least 7 days due to enhanced immunodepletion and T_{reg} depletion therapy. Williams *et al*. evaluated a Phase I trial of irradiated NK-92 cell therapy in 12 patients with relapsed hematological malignancies after autologous

hematopoietic cell transplantation [75]. The clinical outcome showed that five patients had remission and improvement, and no serious adverse events occurred.

Similarly to CAR-T, CAR-NK cellular treatment against specific antigens is introduced to attack tumor cells. Currently, several preclinical researches have assessed the feasibility of CAR-NK cells in the field of malignant lymphoma, such as anti-CD20 CAR-NK cells against lymphoma cells *in vitro* [76,77] and a Burkitt's lymphoma mouse model *in vivo* [77], anti-CD3 CAR-NK-92 cells against peripheral T cell lymphoma [78], anti-CD19 CAR-NK-92 cells against B cell lymphoma [79], anti-CD4 CAR-NK-92 cells against T cell lymphoma [80], anti-CD5 CAR-NK cells against T cell malignancies [81] and anti-38 CAR-NK-92 cells against Burkitt's lymphoma cells [82]. A clinical trial investigated by Liu *et al.* has shown the effectiveness and safety of anti-CD19 CAR-NK cell therapy in 11 relapsed or refractory CD19-positive hematological neoplasms, including six NHL patients and five chronic lymphocytic leukemia patients. A total of eight patients achieved remission response within 1 month after CAR-NK treatment and the duration of CAR-NK cells *in vivo* was at least 12 months [83].

Discussion

With the rapid development of basic and clinical research of malignant lymphoma, clinical trials of immunotherapy for malignant lymphoma are gradually emerging and bring more benefits to targeted patients. However, therapeutic efficacy is limited in certain types of lymphoma, and adverse events cannot be ignored. For PD-1/PD-L1 inhibitors, the most common drug-related toxicities were fatigue, nausea and diarrhea, which were tolerated and manageable. For other immune checkpoints, such as CTLA-4, TIGIT, TIM-3 and LAG-3, preclinical studies of their inhibitors have demonstrated feasibility, while related clinical trials are ongoing and efficacy and safety remain to be determined. For cellular treatment, donor source and cell infusion-related complications should be thoroughly considered and solved. Despite some encouraging clinical results from cellular treatment, large-scale studies need to be carried out to further support these results. In future, ICIs combined with cellular treatment, such as combination of PD/PD-L1 inhibitors and CAR-T cell therapy, might further enhance anti-lymphoma activity. Extensive clinical trials are ongoing to provide optimal strategies and improve the prognosis for lymphoma patients.

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Disclosures

The authors have no conflicts of interest to declare.

Author contributions

F. L. proposed the idea for this study and revised the paper. F. L. and Y. C. collected the literature and wrote the initial paper. M. P. and P. Y. reviewed the literature and provided suggestions for revision. H. J. had primary responsibility for the final content.

Data Availability Statement

All data used in the study are available online or from the corresponding author on reasonable request.

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