Immune targeted therapy for diffuse large B cell lymphoma

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Abstract

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin lymphoma, is highly heterogeneous and invasive. Although the majority of DLBCL patients show a good response to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone treatment, approximately one-third of patients still have a poor prognosis. Many immune-targeted drugs, such as bispecific T-cell engagers and CAR T-cell therapy, have been proven effective for refractory and relapsed patients. This article reviews the progress of immune targeted therapy for DLBCL.

Keywords: Antibody-drug conjugates, Checkpoint inhibitors, DLBCL, Monoclonal antibodies, Signaling pathway inhibitors

1. INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for 30% to 40% NHL patients according to worldwide data.[1] Next-generation sequencing has enabled the elucidation of the remarkable complexity of DLBCL, and some molecular targets with therapeutic potential have been identified. The continuous advancement of targeted therapy has proven that many monoclonal antibodies (MoAbs)-based drugs targeting CD20, CD38, CD22, and CD79b have significant effects on DLBCL.[2]

Immune checkpoint-, tumor microenvironment-, and epigenetic regulation-related therapy have also shown clinical effectiveness. In this paper, we mainly discuss the strategies and latest progress of DLBCL treatment from the perspective of MoAbs, antibody-conjugated drugs, signaling pathway inhibitors, immune checkpoint inhibitors, and epigenetic regulation aimed at improving DLBCL prognosis (Fig. 1).

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2. MoAb-BASED DRUGS

The first mouse-derived MoAb muromonab-CD3 was approved by the US Food and Drug Administration (FDA). The main mechanisms of MoAb include apoptosis induction, antibody-dependent cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC).

2.1. CD20 MoAbs

CD20, which is expressed on all B cell surfaces, plays an important role in the proliferation, activation, and cell cycle of human B cells. According to their distinct mechanisms, CD20 MoAbs can be classified into 2 types. Type I CD20 MoAbs, such as rituximab and ofatumumab, effectively activate the complement system and induce CDC, whereas type II agents, such as obinutuzumab, significantly initiate programmed cell death through both apoptotic and non-apoptotic mechanisms.[3]

Rituximab (R) is a human-murine chimeric anti-CD20 MoAb, while second-generation MoAbs are partially (-zumab) or completely (-mumab) humanized. Ofatumumab (O-), which has been approved for refractory chronic lymphocytic leukemia (CLL), has also shown great potential in other B cell NHL, such as follicular lymphoma (FL) and DLBCL. A study compared the efficacy of O versus R combined with cisplatin, cytarabine, and dexamethasone (DHAP) in relapsed or refractory (R/R) DLBCL patients[4] and found no difference. More clinical trials are needed to prove its efficacy.

Obinutuzumab (G) is a humanized type II anti-CD20 MoAb that has been approved by FDA for CLL in combination with chlorambucil, and has shown superior antitumor activity compared to R in xenograft models.[5] A randomized phase III study demonstrated a similar prognosis for DLBCL patients treated with G-CHOP or R-CHOP.[6] Another phase II multicenter study showed an objective response rate (ORR) and complete

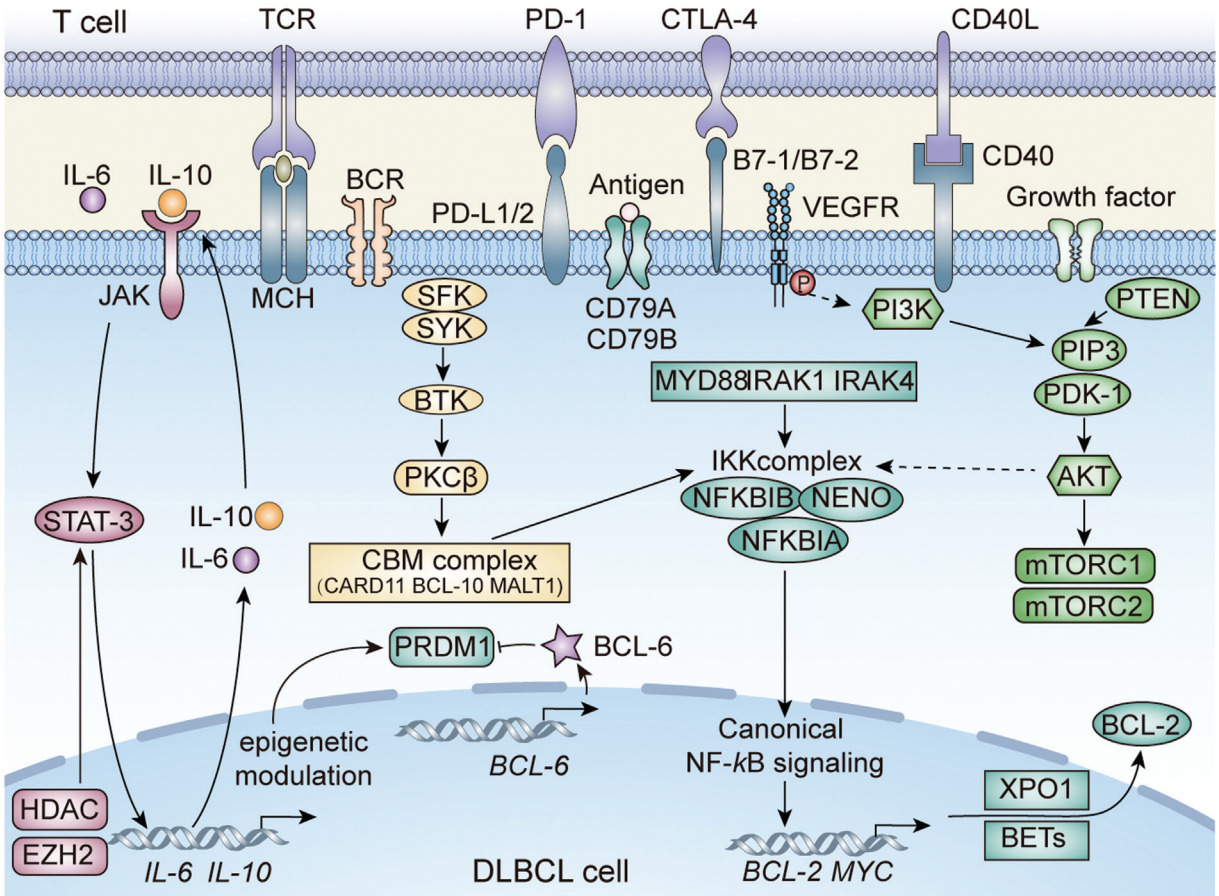

Figure 1. Schematic mechanism of immune targeted therapy for DLBCL. There are numerous molecular pathways and their genomic alterations in DLBCL that contribute to its initiation, maintenance, and progression. Activation or deactivation of these molecular pathways affects epigenetic control, proliferation, differentiation, and apoptosis. Targeting these small molecules may provide a more effective treatment. DLBCL=diffuse large B-cell lymphoma.

response rate (CRR) of 75.0% and 58.0%, respectively, in CD20-positive DLBCL patients treated with G-CHOP, indicating its clinical benefits as a first-line treatment.[7]

2.2. CD19 MoAbs

CD19, a type I transmembrane protein belonging to the immunoglobulin (Ig) superfamily, is specifically expressed in both normal and neoplastic B cells, as well as follicular dendritic cells. Tafasitamab (MOR208), a humanized Fc-enhanced anti-CD19 MoAb, has shown preclinical and single-agent activity in R/R B cell NHL, including DLBCL,[8] and is approved to use with lenalidomide. Inebilizumab (MEDI-551) is also a humanized anti-CD19 MoAb proven to be effective against CD19+ B cell lymphomas.[9] A multicenter phase I study of B cell malignancies found that it was effective in R/R FL and DLBCL,[10] indicting its high clinical value in B cell lymphomas expressing CD19.

2.3. CD38 MoAb

CD38 is a multifunctional type II transmembrane glycoprotein that is expressed at low levels in normal hematological cells, whereas expressed high in plasma cells and some hematological tumors, providing a novel theoretical basis for DLBCL treatment. Daratumumab (Darzalex) is a humanized CD38 MoAb with antitumor activity in B cell NHL,[11] suggesting a potential clinical use in combination with salvage chemotherapy in DLBCL.

2.4. CD22 MoAb

CD22, commonly classified as an inhibitory receptor, is not only associated with B cell receptor (BCR) but also induces B cell responses. CD22 is highly expressed in both mature and malignant B cells, making it a target for B cell lymphoma treatment.

Epratuzumab is a humanized monoclonal IgG1 antibody that acts mainly through the induction of ADCC, CDC, and apoptosis. A phase II study reported that epratuzumab (360 mg/m^2) combined with rituximab in R/R NHL patients resulted in complete response (CR).[12] Another phase II trial evaluated the safety and efficacy of epratuzumab with R-CHOP in DLBCL patients, and found that the 3-year event-free survival (EFS) and overall survival (OS) were 70% and 80%, respectively.[13]

2.5. CD52 MoAb

CD52, a costimulatory molecule that induces T regulatory cells, is expressed in a variety of normal and malignant lymphocytes. However, its expression in DLBCL was significant heterogeneity. Alemtuzumab is a humanized anti-CD52 MoAb that recognizes the CD52 antigen expressed on both malignant and normal B lymphocytes. A study showed that of the 11 DLBCL patients who received chemotherapy combined with alemzumab, 62.5% achieved partial response (PR), confirming the efficacy of alezumab for B cell malignancies.[14]

2.6. CD40 MoAb

CD40, expressed on antigen-presenting cells such as dendritic cells, B cells, and monocytes, as well as leukemia and lymphoma cells, is a member of the tumor necrosis factor receptor (TNF) superfamily. Dacetuzumab is a humanized anti-CD40 MoAb that has antitumor effects against DLBCL with or without other drugs.

A phase Ib study of dacetuzumab combined with rituximab and gemcitabine in R/R DLBCL patients showed CR and PR in 6 and 8 patients, with an ORR of 47%.[15] Although dacetuzumab alone showed antitumor activity in DLBCL patients, preclinical and clinical data indicated that improved antitumor activity was seen when combined with other drugs (Table 1).[16]

3. ANTIBODY-DRUG CONJUGATES

Antibody drug conjugates (ADCs) are MoAbs that are specific to tumor cell surface proteins and conjugated to small molecules with high cytotoxicity, which results in improved efficacy, reduced toxicity, preferable pharmacodynamics, and biodistribution.[17]

3.1. Anti-CD30 ADC

Brentuximab vedotin (BV), formed by an anti-CD30 MoAb and a microtubule rupture agent monomethyl auristatin E, has been approved for classical Hodgkin lymphoma.[18] A phase II study evaluating the efficacy of BV monotherapy in DLBCL patients demonstrated a higher ORR,[19] providing a new treatment option for refractory DLBCL patients.

3.2. Anti-CD79b ADC

Polatuzumab vedotin (Polivy^{TM}) is composed of a MoAb that recognizes CD79b and a microtubule that destroys the antimitotic agent methyl calendulin (MMAE).[20] This agent is approved for R/R DLBCL in combination with bendamustine and rituximab. An open-label phase Ib/II study evaluated the safety and preliminary activity of polatuzumab vedotin combined with immunotherapy in previously untreated DLBCL patients[21] and the results showed an ORR of 89%, including 77% CR and 12% PR.

3.3. Anti-CD22 ADC

Inotuzumab ozogamicin (INO) is a CD22-directed ADC that has been approved for R/R CD22+ precursor B cell lymphoblastic leukemia. A phase I/II study evaluating the safety and efficacy of INO plus rituximab in R/R B-cell NHL showed an ORR of 74% in relapsed DLBCL patients,[22] demonstrating a great clinical benefit.

3.4. Anti-CD19 ADC

Loncastuximab tesirine (ADCT-402), which contains a CD19-targeting antibody, shows potent and highly targeted cytotoxicity against CD19-expressing cell lines.[23] A multicenter phase I study enrolled 88 patients to evaluate the safety and clinical activity of loncastuximab tesirine in B-cell NHL.[24] The results showed an ORR of 45.6%, including 26.7% CR, whereas the ORR in DLBCL was up to 42.3%.

4. BISPECIFIC T-CELL ENGAGERS

Bispecific T-cell engagers (BiTEs) are novel immunotherapy molecules to direct T-effector memory, binding to T cell-specific molecules and tumor-associated antigens.[25] BiTEs are considered to be one of the most promising treatment strategies.

Blinatumomab is a bispecific CD19/CD3-directed T-cell engager that has been approved for R/R Philadelphia chromosome (Ph)-negative acute lymphoblastic leukemia (ALL). A phase I study enrolled 76 R/R NHL patients, including 14 DLBCL, to evaluate the effect of blinatumomab ($60\,\mu g\,m^{(2)-1}$ day).[26] In this study, the ORR of all patients was 69%, whereas that of DLBCL patients was 55%, demonstrating a promising anti-lymphoma activity of blinatumomab.

Glofitamab, a CD20/CD3 antibody, is undergoing several clinical trials. A phase Ib trial (NCT03467373) evaluating glofitamab in untreated DLBCL and a phase III trial (NCT04408638) comparing glofitamab versus rituximab combined with GemOx in R/R DLBCL are ongoing.

Mosunetuzumab (RG7828, RO7030816) is a bispecific CD20/CD3 antibody. In a phase I/II trial (NCT03677154), mosunetuzumab monotherapy in DLBCL received 58% ORR and 42% CR. The combination of mosunetuzumab and CHOP in a phase Ib/II study (NCT03677141) showed 96% ORR and 85% CR in DLBCL.

Based on the existing clinical studies, we can preliminarily believe that BiTEs have a good prospect in the clinical application of DLBCL.

5. SIGNALING PATHWAY INHIBITORS

Signaling pathways are generally considered as enzymatic reaction pathways which transmit extracellular molecular signals to intra-cells and are involved in numerous essential biological processes, such as cell proliferation, differentiation, and apoptosis.

5.1. Proteasome inhibitor

Proteasomes play an essential role in cell survival, DNA repair, degradation of abnormal proteins, and proliferation of malignant cells. Proteasome inhibitors are widely used in hematologic malignancies and have proven to significantly improve prognosis. Due to the wide application of proteasome inhibitors in therapy, we list the relevant clinical trials in Table 2.

5.1.1. First-generation proteasome inhibitors. Bortezomib is a selective 26S proteasome inhibitor with anti-proliferative and antitumor activity, and it has effects on cell proliferation, apoptosis, and angiogenesis.[27] Bortezomib has been approved to treat multiple myeloma (MM) and mantle cell lymphoma (MCL). A global clinical trial recruited 49 patients to investigate whether the addition of bortezomib to doxorubicin-based chemotherapy could improve the survival of DLBCL.[28] The results showed that bortezomib alone had no activity, while a higher response rate (83% vs 13%) and longer OS (10.8 vs 3.4 months) were observed in patients treated with bortezomib combined with chemotherapy. Another multicenter study also demonstrated 100% ORR with 86% CRR in DLBCL patients coadministered with bortezomib and R-CHOP, whereas the 2-year PFS and OS rates were 64% and 70%, respectively.[29] However, an open-label randomized phase 3 trial showed the addition of bortezomib did not improve patients' PFS.

5.1.2. Second-generation proteasome inhibitor. Carfizomib (CFZ), a second-generation proteasome inhibitor, has shown significant clinical activity alone and in combination with other drugs. A study found that CFZ alone or combined

Table 1

Clinical trails of monoclonal antibodies.

Drug	Type	Disease	Trail	NCT	ORR/CR
Obinutuzumab	CD20 antibody	Relapsed or refractory DLBCL	A dose-escalating study of obinutuzumab in patients with B-lymphocyte antigen (CD20+) malignant disease.	NCT00517350	ORR 28% CR 4%
Ublituximab	CD20 antibody	DLBCL	Study of humanized anti-CD20 in patients with CD20+ non-Hodgkin lymphoma.	NCT 00285428	ORR 43% CR 0%
Epratuzumab	CD22 antibody	Relapsed or refractory DLBCL	Epratuzumab, a humanized anti-CD22 antibody, in aggressive non-Hodgkin lymphoma: phase I/II clinical trial results.	_	ORR 15% CR 9%
Epratuzumab with R-CHOP	CD22 antibody combination	DLBCL	Monoclonal antibody therapy and combination chemotherapy in treating patients with stage II, stage III, or stage IV diffuse large B-cell lymphoma.	NCT00301821	ORR 96% CR 74%
Inotuzumab ozogamicin and rituximab	CD22 ADC	Relapsed DLBCL	Study evaluating inotuzumab ozogamicin administered in combination with rituximab in subjects with non-Hodgkin lymphoma.	NCT00299494	ORR 74% CR 50%
Inotuzumab ozogamicin R-CVP vs R-G-CVP	CD22 ADC combination	DLBCL	Treatment of patients with diffuse large B-cell lymphoma who are not suitable for anthracycline-containing chemotherapy.	NCT01679119	In the start
Polatuzumab vedotin, rituximab	CD79 ADC or combination	DLBCL	A study of escalating doses of polatuzumab vedotin in patients with relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia and polatuzumab vedotin with rituximab in participants with relapsed or refractory B-cell non-Hodgkin lymphoma.	NCT01290549	Single agent polatuzumab vedotin ORR56% CR 16% R-pola ORR 78% CR 22%
Pinatuzumab vedotin, obinutuzumab, polatuzumab vedotin, and rituximab	CD79 ADC	Relapsed or refractory DLBCL	A study of pinatuzumab vedotin combined with rituximab or polatuzumab vedotin combined with rituximab or obinutuzumab in participants with relapsed or refractory B-cell non-Hodgkin lymphoma.	NCT01690898	pina ORR60% CR 26% R-pola ORR 54% CR 21%
Polatuzumab vedotin, rituximab or bendamustine, and obinutuzumab	CD79 ADC	Relapsed or refractory DLBCL	A study of polatuzumab vedotin in combination with rituximab or obinutuzumab plus bendamustine in patients with relapsed or refractory FL or DLBCL.	NCT02257567	In the start
Polatuzumab vedotin, R-CHP Vs R-CHOP	CD79 ADC combination	DLBCL	A study comparing the efficacy and safety of polatuzumab vedotin with rituximab-cyclophosphamide, doxorubicin, prednisone, versus rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone in participants with diffuse large B-cell lymphoma.	NCT03274492	Recruiting
Inebilizumab	CD19 antibody	Relapsed or refractory B-NHLs	A phase 1, dose-escalation study of inebilizumab in Japanese adult with relapsed or refractory advanced B-cell malignancies.	NCT01957579	DLBCL ORR 50% CR 17%
Inebilizumab, ICE/DHAP vs rituximab, ICE/DHAP	CD19 antibody	Relapsed or refractory DLBCL	A phase 2, multicenter, randomized, open-label study of inebilizumab in adults with relapsed or refractory DLBCL.	NCT01453205	Inebilizumab (2 mg/kg), ICE/DHAP ORR 46.2% inebilizumab (4 mg/kg), ICE/DHAP ORR 43.6% rituximab, ICE/DHAP ORR 47.5%

(*continued*)

Table 1
(continued).

Drug	Type	Disease	Trail	NCT	ORR/CR
Tafasitamab	CD19 antibody	Relapsed or refractory NHLs	Study of Fc-optimized anti-CD19 antibody tafasitamab to treat non-Hodgkin lymphoma.	NCT01685008	ORR 26% CR 6%
Tafasitamab	CD19 antibody	Relapsed or refractory DLBCL	A study to evaluate the safety and efficacy of tafasitamab with lenalidomide in patients with relapsed or refractory DLBCL.	NCT02399085	ORR 58% CR 33%
Tafasitamab with bendamustine vs rituximab with bendamustine	CD19 antibody combination	Relapsed or refractory DLBCL	A trail to evaluate the efficacy and safety of tafasitamab with bendamustine versus rituximab with bendamustine in adult patients with relapsed or refractory DLBCL.	NCT02763319	Recruiting
Coltuximab ravtansine	CD19 ADC	Relapsed or refractory DLBCL	Coltuximab ravtansine as single agent in relapsed or refractory DLBCL patients.	NCT01472887	ORR 43.9% CR 14.6%
Ioncastuximab tesirine	CD19 ADC	Relapsed or refractory DLBCL	Study to evaluate the efficacy and safety of ioncastuximab tesirine in patients with relapsed or refractory DLBCL.	NCT03589469	In the start
Ioncastuximab tesirine and ibrutinib	Combination	DLBCL	Safety and antitumor activity study of ioncastuximab tesirine plus ibrutinib in diffuse large B-cell or mantle cell lymphoma.	NCT03684694	Recruiting
Ioncastuximab tesirine and durvalumab	Combination	DLBCL/MCL/FL	Safety and antitumor activity study of ioncastuximab tesirine and durvalumab in diffuse large B-cell, mantle cell, or follicular lymphoma.	NCT03685344	Recruiting
Dacetuzumab	CD40 antibody	Relapsed DLBCL	Study of dacetuzumab in patients with relapsed diffuse large B-cell lymphoma.	NCT00435916	ORR 9% CR 4%
Dacetuzumab, R-ICE vs placebo, R-ICE	Combination	Relapsed DLBCL	A randomized phase 2 placebo-controlled study of R-ICE chemotherapy with and without dacetuzuma for patients with DLBCL	NCT00529503	Dacetuzumab, R-ICE ORR 66% CR 33% placebo, R-ICE ORR 64% CR 36%
Blinatumomab	CD19/CD3 BiTE	Relapsed NHLs	Safety study of the bispecific T-cell engager blinatumomab in patients with relapsed NHLs.	NCT00274742	DLBCL ORR 55% CR 36%
Blinatumomab	CD19/CD3 BiTE	Relapsed DLBCL	Clinical study with blinatumomab in patients with relapsed diffuse large B-cell lymphoma.	NCT01741792	ORR 43% CR 19%
Mosunetuzumab	CD20/CD3 BiTE	DLBCL	A trail of mosunetuzumab as consolidation therapy in 1/2 participants with diffuse large B-cell lymphoma following first-line immunochemotherapy and as therapy in participants with previously untreated diffuse large B-cell lymphoma who are unable to tolerate full-dose chemotherapy	NCT03677154	Recruiting
Mosunetuzumab and polatuzumab vedotin	CD20/CD3 BiTE combination	B-cell NHLs	A study to evaluate the safety and efficacy of mosunetuzumab in combination with polatuzumab vedotin in B-cell NHLs.	NCT03671018	Recruiting

with BV6, a second mitochondria-derived activator of caspases mimetic, reduced cell viability, induced apoptosis, and initiated the accumulation of NOXA, which was necessary for cell death.[30] Carfizomib alone (NCT01336920) or combined with R-CHOP (NCT02073097), vorinostat (NCT01276717), and umbralisib (NCT02867618) in R/R lymphoma are still ongoing.

Ixazomib is an oral second-generation proteasome inhibitor approved to treat R/R MM patients. A study on the preclinical and biological effects of ixazomib indicated that ixazomib has effective antitumor activity against DLBCL,[31] offering a more efficient therapy for R/R DLBCL. The efficacy of ixazomib in combination with rituximab (NCT02339922) or ibrutinib (NCT03323151) is currently being evaluated in indolent B-NHLs.

The combination of proteasome inhibitors and chemotherapy has shown great clinical efficacy in clinical trials, and its clinical application is worthy of further promotion.

Table 2

Clinical trails of proteasome inhibitors.

Drug	Type	Disease	Trail	NCT	ORR/CR
Bortezomib	Proteasome inhibitor	Non-GCB DLBCL	A study of bortezomib plus GDP in the treatment of relapsed or refractory non-GCB DLBCL.	NCT02542111	–
Carfilzomib and R-CHOP	Proteasome inhibitor combination	DLBCL	Carfilzomib and rituximab, and combination chemotherapy in treating patients with diffuse large B-cell lymphoma.	NCT0203097	Recruiting
Carfilzomib and R-ICE	Proteasome inhibitor combination	Relapsed or refractory DLBCL	Carfilzomib, rituximab, ifosfamide, carboplatin, and etoposide in treating patients with relapsed or refractory DLBCL.	NCT01959698	Recruiting
Ixazomib and rituximab	Proteasome inhibitor combination	Indolent B-NHLs	Ixazomib and rituximab in treating patients with indolent B-NHLs.	NCT02339922	Recruiting
lenalidomide, ixazomib and rituximab	Proteasome inhibitor combination	High-risk indolent B-NHLs	Lenalidomide, ixazomib, and rituximab as frontline therapy for high-risk indolent B-NHLs.	NCT02898259	In the start

5.2. Bruton tyrosine kinase inhibitors

Bruton tyrosine kinase (BTK) plays a crucial role in the oncogenic signaling of BCR and other receptors essential for the survival and proliferation of lymphoma cells. The BCR signaling pathway is activated in secondary lymphatic organs and drives the proliferation of malignant B cells.[32] Thus, blocking this pathway provides a novel promising treatment for B cell malignancies. The BTK inhibitor-related clinical trials are listed in Table 3, aiming to provide an intuitive and clear experimental reference for the choice of the drug combination. Table 3 indicates that BTK inhibitors are less effective in treating untreated non-GCB DLBCL, and the clinical trials of its combination therapy are still ongoing.

5.2.1. Ibrutinib. Because of its high selectivity and potency, ibrutinib has become a new option for R/R NHL patients. A phase I study evaluated ibrutinib combined with rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) in DLBCL and

Table 3

BTK inhibitor-related clinical trails.

Drug	Type	Disease	Trail	NCT	ORR/CR
Ibrutinib	BTK inhibitor	Relapsed or refractory DLBCL	Safety and efficacy study of a Bruton tyrosine kinase inhibitor in subjects with relapsed or refractory diffuse large B-cell lymphoma.	NCT01325701	ABC-DLBCL 37%/16% GCB-DLBCL 5%/0%
Ibrutinib	BTK inhibitor	Relapsed or refractory B-NHLs	Study of the safety and tolerability of ibrutinib in patients with recurrent B-cell lymphoma.	NCT00849654	ORR 60% CR 16%
Ibrutinib and nivolumab	BTK inhibitor combinatin	Relapsed or refractory B-NHLs, CLL/SLL	A study to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of the combination of ibrutinib with nivolumab in participants with hematologic malignanices.	NCT02329847	DLBCL 36%/16%
Ibrutinib, lenalidomide and rituximab	BTK inhibitor combination	Untreated and unfit elderly DLBCL	Study evaluating the safety and efficacy of ibrutinib, lenalidomide, and rituximab in untreated and unfit elderly patients with DLBCL.	NCT03949062	Recruiting
Ibrutinib, R-CHOP vs placebo, R-CHOP	BTK inhibitor combination	Untreated non-GCB DLBCL	A study of Bruton tyrosine kinase inhibitor, ibrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in patients with newly diagnosed non-germinal. center B-cell subtype of diffuse large B-cell lymphoma.	NCT01855750	Ibrutinib, R-CHOP ORR 67.3% placebo, R-CHOP ORR 68%
Acalabrutinib and R-CHOP	BTK inhibitor combination	Untreated DLBCL	A combination of acalabrutinib with R-CHOP for patients with diffuse large B-cell lymphoma.	NCT03571308	Recruiting
Acalabrutinib and R-ICE	BTK inhibitor combination	Relapsed or refractory DLBCL	Acalabrutinib plus R-ICE for relapsed or refractory diffuse large B-cell lymphoma.	NCT03736616	Recruiting
Zanubrutinib	BTK inhibitor	Relapsed or refractory non-GCB DLBCL	Study of BTK inhibitor zanubrutinib in subjects with relapsed or refractory non-GCB type diffuse large B-cell lymphoma.	NCT03145064	In the start
Vecarutinib	BTK inhibitor	B-NHLs	Safety and antitumor activity of vecarutinib in B-lymphoid cancers.	NCT03037645	Recruiting

Table 4

The SYK inhibitor-related clinical trails.

Drug	Type	Disease	Trail	NCT	ORR/CR
Fostamatinib	SYK inhibitor	Relapsed or refractory B-cell lymphoma	Efficacy and safety of fostamatinib tablets to treat B-cell lymphoma.	NCT00446095	ORR 22%
TAK-659	SYK inhibitor	Relapsed or refractory DLBCL	TAK-659 in participants with relapsed or refractory diffuse large B-cell lymphoma.	NCT03123393	In the start
TAK-659 and R-CHOP	SYK inhibitor combination	High-risk DLBCL	Combination chemotherapy and TAK-659 as frontline treatment in treating patients with high-risk DLBCL.	NCT03742258	Recruiting

demonstrated that out of 20 patients, 11 and 7 patients achieved CR and PR, respectively, with an ORR of 90%.[33] A recent clinical study demonstrated that ibrutinib plus lenalidomide and rituximab has promising activity in R/R non-GCB DLBCL, and the phase 2 trial is currently ongoing (NCT02077166). However, in a phase III study (NCT01855750), ibrutinib combined with R-CHOP produced a CR rate of 67.3% in untreated non-GCB DLBCL patients, which showed no statistically significant difference compared with the placebo plus R-CHOP group. Therefore, the application of ibrutinib in DLBCL still needs a large number of clinical trials to be verified.

5.2.2. Zanubrutinib. Zanubrutinib, an oral BTK inhibitor, has been approved to treat adult MCL patients who have received at least 1 prior therapy. However, the clinical effect of this agent in DLBCL has not been confirmed. A phase 2 trial of zanubrutinib in R/R DLBCL (NCT03145064), and the combination study of zanubrutinib with other drugs (NCT04668365) are still ongoing.

5.2.3. Tirabrutinib. Tirabrutinib is an oral second-generation BTK inhibitor that has comparable efficacy and reduced toxicity compared to ibrutinib, and is approved for primary central nervous system (CNS) lymphoma.[34] A preclinical study showed that tirabrutinib induced a more intuitive response in ABC-DLBCL cell lines than ibrutinib did.[35] The synergistic action of idelalisib or entospletinib combined with tirabrutinib is currently under phase Ib evaluation (NCT02457598).

5.2.4. Acalabrutinib. Acalabrutinib, a second-generation inhibitor, has been approved by the FDA to treat MCL. An open-label phase Ib/II trial testing the safety and efficacy of adding acalabrutinib to R-CHOP in newly diagnosed DLBCL patients determined the recommended dose to be 100 mg.[36]

5.3. Spleen tyrosine kinase inhibitors

Spleen tyrosine kinase (SYK) is an important non-receptor tyrosine kinase that acts as both a tumor promoter and suppressor in hematological malignancies through various immune-recognizing receptors that mediate BCR and TCR signals. The SYK inhibitor-related clinical trials are summarized in Table 4, to demonstrate more intuitionistic clinical trial evidence for the selection of drugs.

5.3.1. Fostamatinib disodium. Fostamatinib disodium, an oral SYK inhibitor, is approved to treat thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura. A phase I/II clinical trial of fostamatinib disodium for recurrent B cell NHL enrolled 68 patients, and the results showed an ORR of 22% and 10% in DLBCL and FL, respectively, at a dose of 200 mg twice a day.[37] In unselected R/R DLBCL patients treated with fostamatinib disodium, the ORR was 25% to 30%.

5.3.2. Entospletinib. Entospletinib (GS-9973), an oral second-generation inhibitor of SYK, has a higher selectivity and fewer adverse reactions compared to fostamatinib disodium. Entospletinib monotherapy (800 mg twice daily) was shown to have modest activity in R/R DLBCL patients in a multicenter phase II study.[38] More clinical trials of combination treatment are needed to provide efficacy.

5.3.3. Dual SYK inhibitors. TAK-659 is an SYK/FLT3 dual inhibitor with preclinical activity in B cell malignancy models.[39] A first-in-human study aimed at evaluating the clinical activity, safety, and tolerability of TAK-659 in R/R B cell lymphomas demonstrated an ORR of 28% with a 19% CRR in DLBCL patients.[40]

Cerdulatinib (PRT062070) is a novel, orally dual SYK/JAK inhibitor, which is confirmed the antitumor activity in DLBCL cell lines and primary DLBCL cells.[41] A phase I study involving 16 aggressive DLBCL patients showed that cerdulatinib was well tolerated and exhibited promising antitumor activity.[42]

5.4. Phosphoinositide 3-kinase-AKT-mechanistic target of rapamycin pathway inhibitor

The phosphoinositide 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) signaling pathways are crucial to many physiological and pathological processes, including cell proliferation, angiogenesis, metabolism, differentiation, and survival. Inhibiting this pathway has been reported to be beneficial in both lymphoma cell lines and animal models.[43]

5.4.1. PI3Kδ inhibitors. Idelalisib (GS-1101) is a highly specific oral PI3Kδ inhibitor approved to treat relapsed CLL. A previous study described the mechanisms of idelalisib combined with ibrutinib in non-GCB DLBCL models, and significant tumor regression was observed.[44] Another clinical trial (NCT02457598) evaluating the efficacy of idelalisib combined with ibrutinib is under the way.

Umbralisib (TGR-1202) is a novel PI3Kδ inhibitor that has been approved as a promising treatment for R/R marginal zone lymphoma patients. However, related studies of this agent in DLBCL are still rare. Parsaclisib (INCB050465) is a highly selective PI3Kδ inhibitor that demonstrated antitumor activity to improve long-term survival in R/R B-cell NHL patients in a phase I/II study.[45] Another multicenter phase II study evaluating parsaclisib monotherapy in R/R DLBCL patients demonstrated an ORR of 25%,[46] providing a potential new strategy for the treatment of R/R DLBCL patients.

Table 5

The PD-1 inhibitor-related clinical trails.

Drug	Type	Disease	Trail	NCT	ORR/CR
Nivolumab	PD-1 inhibitor	Relapsed or refractory DLBCL	Study of nivolumab in patients with relapsed or refractory diffuse large B-cell lymphoma that have either failed or not eligible for autologous stem cell transplant.	NCT02038933	ASCT-failed, 10.3%/2.9% ASCT-ineligible, 3.4%/0%
Nivolumab	PD-1 inhibitor	Relapsed or refractory NHL	Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase 1 study	NCT01592370	DLBCL 26%/18%
Pembrolizumab	PD-1 inhibitor	Transformed DLBCL /relapsed or refractory CLL	Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL.	NCT02332980	transformed DLBCL 41%/11%
Pembrolizumab	PD-1 inhibitor	Relapsed or refractory GZL/extranodal DLBCL	Pembrolizumab in relapsed or refractory gray-zone lymphoma, primary central nervous lymphoma, and other extranodal diffuse large B-cell lymphoma	NCT03255018	Recruiting
Pembrolizumab and rituximab	PD-1 inhibitor combination	Relapsed or refractory DLBCL/FL	Pembrolizumab and rituximab in treating patients with relapsed or refractory DLBCL or FL	NCT03401853	Recruiting
Pembrolizumab and tisagenlecleucel	PD-1 inhibitor combination	Relapsed or refractory DLBCL	Study of pembrolizumab in combination with tisagenlecleucel in relapsed or refractory DLBCL patients.	NCT03630159	Recruiting

5.4.2. mTOR inhibitors. Temsirolimus selectively inhibits mTOR kinase, thereby blocking the translation of cell cycle regulatory proteins and angiogenic growth factors. A phase I/II trial evaluating the safety and activity of temsirolimus added to R-DHAP as salvage therapy for R/R DLBCL patients is ongoing.[47]

Everolimus is an oral mTOR pathway inhibitor that has been reported to inhibit DLBCL cell growth.[48] A phase I study in untreated DLBCL patients demonstrated that everolimus combined with R-CHOP was effective in both GCB and non-GCB DLBCL patients, with a CRR of 96%.[49]

6. IMMUNE CHECKPOINT AND IMMUNOMODULATOR

6.1. Immune checkpoint inhibitors

Instead of targeting malignant cells directly, immune checkpoint inhibitors stimulate the immune system to play an antitumor role by increasing the cytotoxicity of T cells, thereby blocking the inhibitory signals from tumor cells. Programmed cell death protein 1 (PD-1)/PD-1 ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors are approved for many cancers, and their clinical efficacy in DLBCL is being studied.

6.1.1. PD-1/PD-L1 inhibitors. The PD-1/PD-L1 checkpoint mainly plays a negative regulatory role in T cell activation and facilitates the control of inflammatory responses and maintenance of self-tolerance. PD-L1 is the ligand of PD-1, which is constitutively expressed on macrophages and is rapidly upregulated in tumor cells. Preclinical studies have shown that inhibiting the interaction between PD-1 and PD-L1 can enhance T-cell response and mediate antitumor activity,[50] providing a novel treatment strategy. To more intuitively demonstrate the clinical application research progress of PD-1 and PD-L1 inhibitors, the clinical trials of PD-1 and PD-L1 inhibitors are shown in Table 5. It can be inferred from Table 5 that single-agent PD-1 and PD-L1 inhibitors did not perform well in treating DLBCL, and combination therapies are still ongoing.

Nivolumab is an anti-PD-1 antibody that has been approved for cHL patients. 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.[51] A recent phase II study (NCT02038933) showed that nivolumab monotherapy had good safety but low ORR in DLBCL patients. Clinical trials of nivolumab combined with other immunochemotherapies are still in progress.

Pembrolizumab (Keytruda) is a humanized anti-PD-1 MoAb with excellent antitumor activity in R/R cHL patients.[52] Another study including 30 DLBCL patients, evaluated the efficacy of pembrolizumab (200 mg) with R-CHOP and showed an ORR of 90% and CRR of 77%, suggesting that this combination may be a promising treatment strategy.[53] According to the current clinical trial results, the clinical benefit of anti-PD-1 antibody in DLBCL patients is not obvious.

6.1.2. CTLA-4 inhibitors. CTLA-4, also known as CD152, provides both positive and negative feedback for T cell activation when combined with its costimulatory receptor CD28. Ipilimumab is a MoAb against CTLA-4 for the first-and second-line treatment of MM. A phase I study reported that blocking CTLA-4 signals with ipilimumab at 3 mg/kg had antitumor activity in R/R DLBCL patients and was well tolerated.[54] However, the clinical efficacy of ipilimumab in DLBCL still requires more clinical trials evidence. Tremelimumab, another humanized CTLA-4 MoAb, is under investigation in clinical trials for DLBCL and invasive B-cell lymphoma (NCT02549651, NCT02205333).

6.1.3. Signal-regulatory-protein α-CD47. CD47 is a widely expressed cell receptor that regulates macrophage phagocytes, neutrophil migration, and activation of dendritic cells, T cells and

Table 6
Clinical trails of epigenetic modifications

Drug	Type	Disease	Trail	NCT	ORR/CR
Azacitidine and vorinostat	DNMT inhibitor combination	Relapsed or refractory DLBCL	Study of azacitidine in combination with vorinostat in patients with relapsed or refractory DLBCL	NCT01120834	ORR 6.7%
Azacitidine and R-CHOP	DNMT inhibitor combination	Untreated DLBCL	Phase 1/2 trail of R-CHOP plus azacitidine in diffuse large B-cell lymphoma	NCT01004991	CR 91.7%
Azacitidine and R-ICE	DNMT inhibitor combination	Relapsed or refractory DLBCL	Oral azacitidine plus salvage chemotherapy in relapsed or refractory diffuse large B-cell lymphoma	NCT03450343	Recruiting
Azacitidine and R-GDP	DNMT inhibitor combination	Relapsed or refractory DLBCL	Azacitidine and R-GDP in patients with relapsed or refractory diffuse large B-cell lymphoma	NCT03719989	In the start
Aecitabine and R-CHOP	DNMT inhibitor combination	Untreated DLBCL IPI > 1	Decitabine plus R-CHOP in diffuse large B-cell lymphoma	NCT02951728	In the start
Decitabine and R ± DHAP	DNMT inhibitor combination	Relapsed or refractory DLBCL	A clinical trail of decitabine in relapsed or refractory diffuse large B-cell lymphoma	NCT03579082	Recruiting
Tazemetostat	EZH2 inhibitor	Relapsed or refractory B-NHLs	Open-label, multicenter, phase 1/2 study of tazametostat as a single agent in subjects with advanced solid tumors or with prednisolone in subjects with DLBCL.	NCT01897571	Phase 1, 38%/14%
Vorinostat	HDAC inhibitor	Relapsed or refractory DLBCL	An investigational drug study with vorinostat in relapsed diffuse large B-cell lymphoma.	NCT00097929	5.6%/5.6%
Vorinostat and R-CHOP	HDAC inhibitor combination	Newly diagnosed advanced-stage DLBCL	Vorinostat, rituximab, and combination chemotherapy in treating patents with newly diagnosed stage II, stage III, stage IV DLBCL.	NCT00972578	81%/52%
Belinostat	HDAC inhibitor	Relapsed or refractory aggressive B-NHLs	Belinostat in treating patients with relapsed or refractory aggressive B-NHLs.	NCT00303953	ORR 10.5%
Chidamide	HDAC inhibitor	Relapsed or refractory DLBCL/FL	Chidamide for patients with relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma.	NCT03410004	In the start
Chidamide and VDDT	HDAC inhibitor combination	Relapsed or refractory DLBCL	Chidamide combined with VDDT regimen in the relapsed or refractory diffuse large B-cell lymphoma.	NCT02733380	Recruiting
Chidamide and R-CHOP	HDAC inhibitor combination	Relapsed or refractory DLBCL	Chidamide with R-CHOP redimen for DLBCL patients.	NCT03201471	Recruiting
Chidamide and R-CHOP	HDAC inhibitor combination	Elderly DLBCL	Chidamide plus R-CHOP in elderly DLBCL.	NCT02753647	Recruiting
Chidamide and R-GDP	HDAC inhibitor combination	Relapsed or refractory DLBCL	Chidamide combined with R-GDP in patients with relapsed or refractory diffuse large B-cell lymphoma.	NCT03373019	Recruiting

B cells by interacting with signal-regulatory-protein α (SIRPα) and other ligands.[55] Hu5F9-G4 is a macrophage immune checkpoint inhibitor that blocks CD47 and induces tumor cell phagocytosis. A phase Ib study involving R/R NHL patients (including 15 DLBCL) demonstrated that the ORR and CRR were 71% and 43%, respectively, in DLBCL patients who received Hu5F9-G4 combined with rituximab.[56]

6.2. Immunomodulator

Lenalidomide is an oral immune-modulator that exerts antitumor effects through direct antineoplastic activity, inhibition of tumor cell proliferation, angiogenesis-mediated immunity, and stimulation of T and NK cell-mediated cytotoxicity. A phase I/II study reported that lenalidomide combined with R-CHOP was effective, with ORR > 90%[57] and 86% CR. Now lenalidomide has been widely used in clinical practice and has achieved a good effect.

7. EPIGENETIC REGULATION THERAPY

Epigenetic regulation mainly involves DNA methylation, histone modification, nucleosome remodeling, and RNA-mediated targeting, which regulate many biological processes that affect the occurrence and development of B-NHL. Clinical trials of epigenetic regulation-related drugs are shown in Table 6. Table 6 indicates that DNA methyltransferase inhibitors combined with the R-CHOP regimen have a better effect on untreated DLBCL patients than chemotherapy, however, it seems to work little on R/R DLBCL. HDAC inhibitors have little effect on R/R DLBCL, and the combination therapy is still being studied.

7.1. DNA methyltransferase inhibitors

DNA methyltransferase (DNMT) mediates an essential epigenetic mechanism that controls the proliferation, apoptosis, differentiation, cell cycle, and cell transformation. A previous study found that DNMT1, DNMT3a, and DNMT3b were overexpressed in 48%, 13%, and 45% DLBCL patients, respectively.[58]

Azacitidine is recommended as a front-line treatment for older AML patients, and its use in other lymphomas has been evaluated.[59] The results of azacitidine combined with vorinostat in R/R lymphoma patients showed that the EFR and OS rate at

15 months were 65% and 77%, respectively, among DLBCL patients.[60] Another phase I/II trial (NCT01004991) of azacitidine combined with R-CHOP reported a CRR of 91.7% in untreated DLBCL patients.

Decitabine, also called AzaD, is approved for higher-risk MDS and AML patients who are not suitable for intensive therapy. A preclinical study demonstrated that decitabine combined with sorafenib induces apoptosis of DLBCL cells.[61] Moreover, a phase IV trial exploring the efficacy and safety of decitabine, rituximab, with or without DHAP in R/R DLBCL (NCT03579082) is recruiting.

7.2. Enhancer of zeste homolog 2 (EZH2) inhibitors

EZH2 is a catalytic subunit of polycomb repressive complex 2 (PRC2) and found to exhibit active mutations in NHL. Tazemetostat, a first-in-class EZH2 inhibitor, has clinical activity in mutant FL and DLBCL. A phase Ib study of tazemetostat (800 mg twice daily) plus R-CHOP showed antitumor activity in newly diagnosed DLBCL patients.[62]

7.3. Histone deacetylase inhibitors

Histone deacetylases (HDACs) are essential for the epigenetic regulation of gene expression and control of cellular activities. HDAC inhibitors can be divided into 3 groups according to their specificity: non-selective (vorinostat, belinostat, and panobinostat), selective (romidepsin, entinostat, and ricolinostat), and multi-pharmacological. Vorinostat (Zolinza) has been approved to treat cutaneous T cell lymphoma. A phase I/II trial of vorinostat combined with R-CHOP in newly diagnosed advanced DLBCL patients showed 2-year PFS and OS rates of 73% and 86%, respectively.[63]

Panobinostat (Farydak) is an oral HDAC inhibitor, and it has been approved for recurrent MM patients with bortezomib and dexamethasone. A clinical study demonstrated that the combination of panobinostat and ibrutinib led to stronger inhibition of NF-κB and degeneration of DLBCL xenografts than either agent alone did.[64] A recent clinical study confirmed that administration of panobinostat as a single agent had long-lasting activity in R/R DLBCL patients.

Romidepsin, a selective HDAC inhibitor, is a promising treatment for T cell lymphoma. Preclinical studies have shown that romidepsin induces tumor cell lysis via selective down-regulation of LMP1 and c-myc expression in EBV+ DLBCL.[65] A phase I study of romidepsin, gemcitabine, dexamethasone, and cisplatin combination therapy in DLBCL patients is ongoing (NCT01846390).

Chidamide is the first oral HDAC inhibitor approved for R/R PTCL. The latest experiment showed that the surface expression of CD20 in DLBCL cell lines was significantly increased by chidamide.[66] Furthermore, co-application of chidamide with rituximab significantly enhanced cell death in vitro and in DLBCL xenograft mice.

8. CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY

T cells engineered with a chimeric antigen receptor (CAR), an emerging promising therapy, can bind to the surface antigen of target cells and induce unrestricted major histocompatibility complex (MHC)-mediated killing of tumor cells. CAR-T cell (CAR-T) therapy has greatly changed the treatment pattern of lymphocytic malignancies, especially DLBCL and ALL. And its efficacy in combination with other drugs is being tested in plenty of clinical trials.

8.1. Anti-CD19 CAR-T

Three anti-CD19 CAR-T cells have been approved or developed. Axicabtagene ciloleucel (KTE-C19) is an anti-CD19 CAR-T cell for R/R DLBCL with potent antitumor activity. A multicenter ZUMA-1 trial evaluating the long-term safety and activity of axicabtagene ciloleucel in refractory DLBCL, demonstrated an ORR of 83% with 58% CRR.[67]

Tisagenlecleucel (CTL019), which has been approved by the FDA for precursor B-cell ALL, is recently approved in Europe. An international phase II study of tisagenlecleucel in R/R DLBCL revealed an ORR of 52%, with 12% CRR and 40% PR rate (PRR).[68]

Lisocabtagene maraleucel (liso-cel) is a candidate drug for the treatment of R/R NHL. The ORR and CRR were 73% and 53%, respectively, in DLBCL at a dose of 100×10^6.[69]

8.2. CD19/CD22 dual-targeted CAR-T

AUTO3, the first dual-targeted CAR-T therapy targeting both CD19 and CD22, shows great prospects in R/R DLBCL in an ongoing phase I/II Alexander study (NCT03287817), with the ORR of 75% and CRR of 63%.

Other studies targeting CD20, CD22, and CD30 CAR-T therapy are being conducted.

The results of a recent meta-analysis showed that CAR-T therapy for R/R DLBCL had an overall CRR of 46.8%,[70] and CRR of CD19 group was higher (49.2%) compared to CD20 group (42.2%). However, CAR-T clinical trials are rare in DLBCL, the long-term prognosis and adverse reactions such as cytokine storm still need to be validated in a large number of trials.

9. TARGETED THERAPY OF SPECIFIC ONCOGENES AND PROTEINS

9.1. B cell lymphoma 2 inhibitors

B cell lymphoma 2 (BCL2) is a crucial regulator of apoptosis. Therefore, BCL2 inhibitors are considered potentially effective agents and can be divided into various types according to the different *BCL2* homology (BH) domains.

Venetoclax (ABT-199), an oral BH3 mimetic, specifically inhibits BCL2 protein and is approved as monotherapy for CLL with 17p deletion. A phase Ib study investigating venetoclax combined with R-CHOP or G-CHOP in DLBCL reported an ORR of 87.5% with CRRs of 78.1%, indicating venetoclax was safe and effective in high-grade DLBCL.[71] A phase 2 CAVALLI (NCT02055820) study demonstrated the combination of venetoclax and R-CHOP in DLBDL has manageable myelosuppression and the potential of improved efficacy, particularly in high-risk BCL2+ patients.

9.2. BCL6 inhibitors

BCL6 is considered as a regulator of GCB cell development and function, and it catalyzes epigenetic changes by activating co-inhibitory complexes. A preclinical study found that FX1, a specific BCL6 inhibitor, inhibited ABC-DLBCL cells both in vitro and in vivo.[72]

9.3. MYC inhibitors

The MYC family oncogenes are deregulated in >50% of human cancers which associate with poor prognosis and survival.

Myc plays an important role in many carcinogenic processes through the regulation of proliferation, apoptosis, differentiation, and metabolism. MYC overexpression is associated with not only low responses but also higher CNS recurrence rates in DLBCL.[73] The mitotic spindle-regulatory kinases Aurora A kinase (AAK) and Aurora B kinase are both overexpressed in MYC-associated B cells.

Alisertib is an oral selective AAK inhibitor with preclinical activity against a variety of hematological malignancies. A phase I study of R/R aggressive B cell lymphoma concluded that a combination of alisertib and rituximab with or without vincristine both had clinical activities against non-GCB DLBCL.[74]

9.4. Exportin-1 inhibitors

Exportin-1 (XPO1), also called chromosome region maintain 1, is a eukaryotic output protein associated with a poor prognosis. The XPO1 nuclear output pathway is involved in protein regulation and signal transduction of several key molecules such as p53 and epidermal growth factor. XPO1 is highly expressed in DLBCL, suggesting it could be a new treatment target.

Selinexor is a first-in-class oral XPO inhibitor that is approved for R/R MM and DLBCL in combination with dexamethasone. Recent studies showed that selinexor monotherapy induced a durable response in R/R DLBCL,[75] with an ORR of 29% including 12% CRR and 17% PRR.

10. CONCLUSION

With the deepening understanding of the pathogenesis mechanism of DLBCL, many immune-targeted therapies have been investigated and are currently being used. Although these agents have effectively improved the prognosis of DLBCL, adverse reactions and relapses continue to occur. Despite promising trials dedicated to R/R DLBCL patients, the new options may not be easy to achieve a superiority versus the current standard treatment. Identifying therapies that can improve the CRR of first-line treatment and reduce the recurrence rate are still being conducted, and the development of precise treatment for every patient is an ongoing pursuit.

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