

Traditional and emerging therapies for anaplastic large cell lymphoma (Review)

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Abstract. Anaplastic large cell lymphoma (ALCL) is a rare and highly invasive non-Hodgkin's lymphoma. In the past few decades, traditional chemotherapy regimens, such as the cyclophosphamide, vincristine, doxorubicin and prednisone regimen, have been recommended for first-line treatment. In order to improve the survival of patients, dose-intensive chemotherapy and hematopoietic stem cell transplantation have been deeply studied and some progress has been made. Recently, with the accumulation of clinical cases and the development of clinical trials, as well improvements to our in-depth understanding of the biological behavior of ALCL, the signaling pathways and the immunotherapy involved, research on this topic is in full swing. The emergence of several targeted drugs and immunotherapies, including anaplastic lymphoma kinase inhibitors, brentuximab vedotin, mTOR inhibitors, programmed cell death protein 1/programmed death ligand 1 inhibitors and chimeric antigen receptor-T cell therapy, seems to provide new opportunities for certain patients with ALCL. The present review focuses on the current use of traditional therapy and the treatment prospects of these new drugs in ALCL.

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1. Introduction

Anaplastic large cell lymphoma (ALCL) is a highly aggressive type of T cell lymphoma (TCL) that is characterized by CD30 expression and accounts for ~2% of adult non-Hodgkin's lymphoma (NHL) (1) and 15% of pediatric NHL cases (2). According to the 2017 World Health Organization classification (3), ALCL is divided into anaplastic lymphoma kinase-positive (ALK⁺) ALCL, ALK-negative (ALK⁻) ALCL, primary cutaneous ALCL and breast implant-associated ALCL; the first two types are collectively referred to as systemic ALCL (sALCL). ALK⁺ ALCL accounts for 60-85% of all sALCL cases, and all express ALK fusion proteins, which are transcribed and translated by ALK fusion genes. The most common fusion gene is nucleophosmin (NPM)-ALK, which is formed by translocation of the ALK gene on chromosome 2p23 and the NPM gene on chromosome 5q35 (4). Another 10-20% of ALK⁺ ALCL cases contain variant ALK fusions, such as 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase-ALK (5), TRK-fused gene-ALK (6), tropomyosin 3-ALK (7) and moesin-ALK (8). The majority of patients with ALCL are males presenting with B symptoms and advanced-stage disease. Patients with ALK⁺ ALCL are usually aged <60 years and are younger than patients with ALK⁻ ALCL (9). Due to the rarity of the disease, most of the evidence describing the outcomes and various treatment options for patients with sALCL comes from retrospective studies of invasive lymphoma or TCL. The most effective therapeutic option for sALCL remains under investigation. Although the outcome of ALCL is more favorable than that of peripheral T-cell lymphoma (PTCL)-not otherwise specified (9), the overall survival (OS) rate and progression-free survival (PFS) rate have barely improved in the past 30 years (10), and the outcomes of relapsed or refractory (R/R) patients are not optimistic. With the deepening of our understanding of ALCL biology, an increasing number of potential therapeutic targets and immune checkpoints are being discovered and tested to improve the prognosis. The

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traditional therapeutic strategies and emerging immunotherapies and targeted therapies of sALCL are presented in this review.

2. Chemotherapy

At present, sALCL is mostly treated with the anthracycline-based cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) regimen, but there is no consensus on the standard regimen for sALCL. With this treatment strategy, the prognosis of patients with ALK⁺ ALCL is significantly superior to that of patients with ALK⁻ ALCL. The German High-Grade Non-Hodgkin Lymphoma Study Group evaluated the outcomes of 343 patients with TCL, including 191 patients with ALCL (113 ALK⁻ and 78 ALK⁺). Patients were separated into CHOP and etoposide plus CHOP (CHOEP) regimen groups. For patients aged ≤ 60 and those with normal lactate dehydrogenase levels, the 3-year event-free survival (EFS) rate of the CHOEP regimen was significantly superior to that of the CHOP regimen, but OS rate was not improved. In elderly patients, the addition of etoposide had no obvious effect on prognosis (11). Another pooled analysis of 263 patients with ALK⁺ ALCL found that CHOEP improved both PFS and OS rates. Furthermore, the 5-year cumulative incidence of relapse (IR)/progression was clearly decreased following etoposide-based induction (37 vs. 17%) (12). This study only included patients with ALK⁺ ALCL and had a longer follow-up period, which may be the reason for the benefits observed in not only PFS rate, but also OS rate.

In addition to CHOP or CHOP-like regimens, a number of studies have been conducted on alternative therapies, such as hyperfractionated cyclophosphamide, vincristine, Adriamycin, dexamethasone/methotrexate and cytarabine (hyper CVAD/MA) (13,14), hyper-CHOP (14) and etoposide, ifosfamide and cisplatin-reinforced doxorubicin, bleomycin, vinblastine and dacarbazine (15). Except for hyper CVAD/MA, which is controversial with regards to improving PFS rate (13,14), none of the other treatments exhibited better outcomes. Although intensive regimens may have a higher response rate, they also lead to a higher toxicity compared with traditional chemotherapy. In addition, due to the rarity of the disease, none of these studies analyzed the individual survival outcomes of ALCL, which needs to be verified by more rigorous randomized controlled trials.

To date, CHOP remains the recommended first-line treatment option for patients with sALCL. Young patients (≤ 60 years old) have a more favorable EFS following the CHOEP regimen, while dose-intensive CHOP or alternative treatments have not been reported to have superior outcomes (Table I). Although patients with ALCL have a more favorable OS and EFS than other patients with PTCL, the effect of traditional chemotherapy has seen little improvement over the past 30 years.

3. Hematopoietic stem cell transplantation (HSCT)

The complete remission (CR) rates of patients with ALK⁺ and ALK⁻ ALCL following first-line treatment are 86 and 68%, respectively (16), but $>40\%$ of patients with ALCL relapse (9,17), and the outcomes of patients with recurrence

remain poor. Studies have explored the effects of high-dose chemotherapy/autologous stem cell transplantation (HDC/ASCT) treatment in patients with ALCL to decrease relapse after the first remission (18-25). Due to the relatively favorable outcomes of first-line chemotherapy, ASCT is not recommended as the upfront consolidation for patients with ALK⁺ ALCL.

Certain retrospective and prospective studies have shown that consolidative ASCT improves the outcomes of patients with PTCL, including those with ALCL (Table II) (18-25). In addition, based on the results of recent studies, the National Comprehensive Cancer Network (NCCN) guidelines (26) and the clinical practice recommendation of the American Society for Blood and Marrow Transplantation (27) recommend ASCT for most PTCL subtypes that reach the first CR (CR1), including ALK⁻ ALCL, but not ALK⁺ ALCL. However, these studies have certain limitations, as all three prospective studies were single-arm phase II studies and did not use a contemporaneous control group. In addition, patients undergoing ASCT tend to be young and in a generally good condition, but with a more aggressive disease state. In addition, these studies had inconsistent responses to first-line chemotherapy [100% CR or partial response (PR)/CR] and different histological types (including or not including ALK⁺ patients). Furthermore, several recent studies, including a retrospective study (28) and prospective cohort study (29), have shown that ASCT could not improve OS rate in patients with ALK⁻ ALCL, highlighting the need for randomized controlled studies to determine the role of ASCT as first-line consolidation therapy.

The role of ASCT and allogeneic HSCT (allo-HSCT) in patients with R/R ALCL remains unclear. Only a few studies have analyzed the impact of HSCT on the survival of patients with R/R ALCL (Table III). The effectiveness of HSCT as consolidation therapy in R/R ALCL was studied in two retrospective analyses conducted by the European Society for Blood and Marrow Transplantation (30,31). The 3-year cumulative IR, PFS and OS rates were 34, 64 and 73% for patients who had undergone ASCT (30), and 40, 53 and 74% for patients receiving allo-HSCT, respectively (31). The 5-year treatment-related mortality (TRM), IR, OS and EFS rates were 25, 28, 54 and 50%, respectively, in a retrospective study that enrolled 24 patients with R/R ALCL who had undergone allo-HSCT (32). In addition, the 5-year OS rate of patients receiving reduced-intensity condition (RIC) regimens ($n=8$) was reported to be superior to that of patients receiving myeloablative conditioning regimens ($n=30$) (100 vs. 49%; $P=0.018$), which may be associated with the lower TRM of the RIC regimen (33). In addition, the retrospective nature of the study and the small number of patients may have had an impact on the results.

One large multicenter retrospective study from the International Blood and Bone Marrow Transplantation Research Center compared the effect of ASCT and allo-HSCT in 112 patients with ALCL (61 ASCT and 51 allo-HSCT) (34). The results revealed that ASCT had a higher 3-year OS rate (62 vs. 33%; $P=0.0088$) and a lower TRM rate (5 vs. 32%; $P<0.001$) compared with allo-HSCT in patients beyond CR1, but PFS rate and recurrence/progression were not significantly different between the two groups. However, an important limitation of that study was that ALK status was indeterminate.

Table I. Studies on survival following chemotherapy in patients with ALCL.

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+ patients, n	ALK- patients, n	ALK status unknown, n	ORR (CR rate), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
Escalon <i>et al</i>	/	2005	/	CHOP Intensive therapy (hyper-CHOP, hyper-CVAD, etc.)	50 63	26 14	7 5	11 6	8 3	/	/	3-year OS ^a : 62% 3-year OS ^a : 56%	/	(14)
Simon <i>et al</i>	NCT00970385	2010	3	VIP-reinforced-ABVD	43	8	7	1	0	58 (44)	2-year EFS ^a : 45%; 5-year EFS ^a : 32.5 months	Median OS ^a : 42 months	Neutropenia, thrombocytopenia	(15)
				CHOP/21	43	6	3	3	0	70 (35)	2-year EFS ^a : 41%, 5-year EFS ^a : 32 months	Median OS ^a : 42 months	/	
Schmitz <i>et al</i>	/	2010	/	CHOP/CHOEP	343	191	78	113	0	/	3-year EFS: ALK+ 75.8%; ALK- 45.7%	3-year OS: ALK+ 89.8%; ALK- 62.1%	/	(11)
Abramson <i>et al</i>	/	2014	/	CHOP-like therapy Hyper CVAD/MA	237 20	/	/	/	/	69 (58) 85 (80)	3-year PFS ^a : 32% 3-year PFS ^a : 53%	3-year OS ^a : 55% 3-year OS ^a : 49%	/	(13)
Sibon <i>et al</i>	/	2019	/	CHOP CHOEP	98 38	98 38	98 38	0 0	0 0	/	5-year PFS: 57% 5-year PFS: 89%	5-year OS: 69% 5-year OS: 97%	/	(12)

^aResult is for all enrolled patients, not just patients with ALCL. ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ORR, overall response rate; CR, complete remission; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; CHOP, cyclophosphamide, vincristine, doxorubicin and prednisone; CHOEP, cyclophosphamide, vincristine, doxorubicin, etoposide and prednisone; hyper CVAD/MA, hyper fractionated cyclophosphamide, vincristine, Adriamycin, dexamethasone/methotrexate and cytarabine; VIP, etoposide, ifosfamide and cisplatin; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine.

Table II. Studies on survival following ASCT in patients with ALCL.

A, Prospective studies												
First author, year	Number of patients available for analysis	Phase	Histological subtype	Design of the study/the significance of the research	Response rate after induction, %	ASCT rate, %	Survival for the entire cohort, %	Survival for patients treated with ASCT	Survival of patients with ALCL, %	Survival of patients of non-ASCT groups	Evaluation of ASCT as the first-line consolidation therapy	Conclusion (support/ not support) (Refs.)
Corradini <i>et al</i> , 2006	62	2	PTCL-NOS (n=28; 45%), AITL (n=10; 16%), ALK + ALCL (n=19; 31%) ALK- ALCL (n=4; 6%)	ITT analysis	CR, 56; PR, 16; PD, 24	74	12-year OS, 34; 12-year EFS, 30	NA	ALK+ ALCL: 12-year OS, 62; 12-year EFS, 54; ALK-, NA	NA	Up-front HDT and ASCT are feasible, but could induce a high rate of long-term CR only in patients with ALK+ ALCL	Support (18)
d'Amore <i>et al</i> , 2012	160	2	PTCL-NOS (n=62; 39%), ALK- ALCL (n=31; 19%), AITL (n=30; 19%), others (n=37; 23%)	ITT analysis	CR/Cru, 53; PR, 31; PD, 16	72	5-year OS, 51; 5-year PFS, 44	NA	5-year OS, 70; 5-year PFS, 61	NA	Dose-dense induction and HDT/ASCT are a rational up-front strategy in transplantation-eligible patients with PTCL	Support (19)
Reimer <i>et al</i> , 2009; Wilhelm <i>et al</i> , 2016	111	2	PTCL-NOS (n=42; 38%), ALK- ALCL (n=16; 14%), AITL (n=37; 33%), others (n=16; 14%)	ITT analysis	CR, 62; PR, 20; PD, 18	68	5-year OS, 44; 5-year PFS, 39	5-year OS, 57%	NA	5-year OS, 23%	Up-front ASCT can result in long-term remissions in patients with all major subtypes of PTCL and therefore should be part of first-line therapy whenever possible	Support (20,21)
Park <i>et al</i> , 2019	119	NA	PTCL-NOS (n=54; 45%), AITL (n=35; 29%), ALK- ALCL (n=30; 25%)	The first large prospective cohort study directly comparing the survival outcomes in CR1 with or without consolidative ASCT	CR, 100	30	2-year OS, 75; 2-year PFS, 63	2-year OS, 87.8%; median PFS, 57.6 months; median OS, 47.5 months	2-y PFS=100% for ASCT group; 2-y PFS=84% for non-ASCT group; median OS (P=0.39) and PFS (P=0.27) not reached in either group	2-year OS, 70%; 2-year PFS, 67%; median PFS, 47.5 months	In nodal PTCL patients, no statistical difference in survival between the ASCT and non-ASCT groups. However, patients with AITL and/or high-risk features might benefit from consolidative ASCT in CR1	Not support (28)

Table II. Continued.

B. Retrospective studies												
First author, year	Number of patients available for analysis	Phase	Histological subtype	Design of the study/the significance of the research	Response rate after induction, %	ASCT rate, %	Survival for the entire cohort, %	Survival for patients treated with ASCT	Survival of patients with ALCL, %	Survival of patients of non-ASCT groups	Evaluation of ASCT as the first-line consolidation therapy	Conclusion (support/ not support) (Refs.)
Rodriguez <i>et al</i> , 2007	74	NA	PTCL-NOS (n=37; 50%), AILT (n=8; 11%), ALCL (n=23; 31%), others (n=6; 8%)	Study based on patients in CR after induction only	CR, 100	100	5-year OS, 68; 5-year PFS, 63	4-year OS, 90%; 4-year EFS, 67% for all PBSCT patients; 4-year OS, 91%; 4-year EFS, 82% for patients undergoing PBSCT at CR1/PR1	ALK status, NA; 5-year OS, 84; 5-year PFS, 80	NA	Consolidation with ASCT in CR patients increased the OS and PFS when compared with conventional chemotherapy	Support (22)
He <i>et al</i> , 2012	64	NA	100% ALCL (ALK+ 33%, ALK- 22%, ALKu 45%)	48 patients undergoing conventional chemotherapy; 16 patients undergoing PBSCT	CR, 46; PR, 39; SD, 11; PD, 4	The PBSCT type was not explained (ASCT or allo-HSCT)	4-year OS, 90; 4-year EFS, 67e	4-year OS, 90%; 4-year EFS, 67% for all PBSCT patients; 4-year OS, 91%; 4-year EFS, 82% for patients undergoing PBSCT at CR1/PR1	NA	4-year OS, 88%; 4-year EFS, 71%	PBSCT improved the EFS of patients with specific adverse factors compared with conventional chemotherapy, OS was not improved	Partial support (23)
Mehta <i>et al</i> , 2013	65	NA	PTCL-NOS (n=32; 49%), AILT (n=21; 32%), ALK- ALCL (n=12; 18%)	Retrospectively identified PTCL patients with the intention to transplant in CR1	CR, 51; PR, 32; PD, 12. For patients received ASCT: CR, 97; PR, 3	52 ASCT; 8 allo-HSCT	4-year OS, 52; 4-year PFS, 38	4-year OS, 67%; 4-year PFS, 55%	4-year OS, 66.7; 4-year PFS, 50 for HD-ASCT group (n=6); 4-year OS, 50; 4-year PFS, 33 for non-transplant group (n=6)	4-year OS, 67%; 4-year PFS, 30% for allo-HSCT group (n=5); 4-year OS, 27%; 4-year PFS, 17% for non-transplant group (n=26)	Support consolidation of CR1 with transplantation.	Support (24)
Ellin <i>et al</i> , 2014	252	NA	PTCL-NOS (n=109; 43%), AILT (n=47; 19%), ALK- ALCL (n=52; 21%), others (n=44; 17%)	Subgroup ITT-based analysis of an initial real-world study	No data on this specific subgroup eligible for transplant	51 in ITT	No data on this specific subgroup eligible for transplant	5-year OS, 48%; 5-year PFS, 41% in the ITT-ASCT group	NA	5-year OS, 26%; 5-year PFS, 20% in the ITT-no ASCT group	Results support the role of ASCT consolidation for EATL and nodal PTCLs except ALK+ ALCL	Support (25)

Table II. Continued.

B. Retrospective studies												
First author, year	Number of patients available for analysis	Phase	Histological subtype	Design of the study/the significance of the research	Response rate after induction, %	ASCT rate, %	Survival for the entire cohort, %	Survival for patients treated with ASCT	Survival of patients with ALCL, %	Survival of patients of non-ASCT groups	Evaluation of ASCT as the first-line consolidation therapy	Conclusion (support/ not support) (Refs.)
Fossard <i>et al</i> , 2018	269	NA	PTCL-NOS (n=78; 29%), AILT (n=123; 46%), ALK- ALCL (n=68; 25%)	ITT-based large multicentric retrospective study with PSM analysis and Cox proportional hazard model	CR, 81; PR, 19	50 in ITT	5-year OS, 60; 5-year PFS, 45	5-year OS, 59%; 5-year PFS, 46% in the ITT-ASCT group	ASCT ITT yes (n=31) vs. no (n=37): PFS: HR=1.02, P=0.89; OS: HR=1.08, P=0.74	5-year OS, 60%; 5-year PFS, 41% in the ITT-no ASCT group	Does not support the use of ASCT for up-front consolidation for all patients with PTCL-NOS, AITL, or ALK-ALCL with CR/PR after induction	Not support (29)

ASCT, autologous stem cell transplant; ITT, intention-to-treat; CR, complete response; Cru, CR unconfirmed; PR, partial response; PD, progressive disease; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; AILT, angioimmunoblastic T-cell lymphoma; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; CR1, first CR; PR1, first PR; NA, not available; PSM, propensity score matching; ITT, intent-to-treat; ALKu, ALK status unknown; HDT, high-dose therapy; PBSCT, peripheral blood stem cell transplantation; HR, hazard ratio.

Table III. Studies on survival following HSCT in patients with R/R ALCL.

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR rate), %	PFS/EFS, %	OS, %	Adverse events 3-4 grade	(Refs.)
Smith <i>et al</i>	/	2013	/	ASCT	115	61	/	/	61	/	3-year PFS, 55	3-year OS, 68	/	(34)
				Allo-HSCT	126	51	/	/	51	/	3-year PFS, 35	3-year OS, 41	/	
Fukano <i>et al</i>	/	2015	/	ASCT	23	23	/	/	23	/	5-year EFS, 38	5-year OS, 51	/	(32)
				Allo-HSCT	24	24	/	/	24	/	5-year EFS, 50	5-year OS, 54	/	
Fukano <i>et al</i>	/	2019	/	MAC regimen	30	30	/	/	30	/	5-year EFS, 43	5-year OS, 49	/	(33)
				RIC regimen	8	8	5	2	1	100 (100)	5-year EFS, 88	5-year OS, 100	/	
Domingo-Domenech <i>et al</i>	/	2020	/	ASCT	65	65	38	24	3	/	3-year PFS, 64	3-year OS, 73	/	(30)
Domingo-Domenech <i>et al</i>	/	2020	/	Allo-HSCT	44	44	23	20	1	/	3-year PFS, 53	3-year OS, 74	/	(31)

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ORR, overall response rate; CR, complete remission; PFS, progression-free survival; EFS, event-free survival; ASCT, autologous stem cell transplantation; HDT, high-dose therapy; allo-HSCT, allogeneic hematopoietic stem cell transplantation; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

According to the NCCN guidelines, allo-HSCT or HDC/ASCT can be used in patients with R/R ALCL who achieve PR/CR following second-line treatment. However, further in-depth studies comparing allo-HSCT and HDC/ASCT specifically in ALCL are necessary to prove their efficiency. In addition, decreasing the mortality rate and the incidence of side effects of HSCT is also a challenge that needs to be overcome.

4. Immunotherapy and targeted therapy

With the development of biomedicine and the reinvention of tumor therapy, targeted therapy and immunotherapy have gradually become the focus of tumor therapy research and are now playing an increasingly important role in the treatment of tumors, including ALCL. The role of drugs such as brentuximab vedotin (BV), histone deacetylase (HDAC) inhibitors, ALK inhibitors and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors in ALCL have already been widely studied (Table IV), and the ongoing trials are summarized in Table V.

BV. BV (SGN-35) is an antibody-drug conjugate (ADC) against CD30 antigen, expressed in HL and ALCL. BV consists of three parts: An anti-CD30 monoclonal antibody cAC10, antimetabolic drug microtubule polymerization monomethyl auristatin E (MMAE) and valine-citrulline dipeptide as a linker (35). CD30 is a member of the tumor necrosis factor receptor superfamily (36); its expression is limited in normal tissues but high in malignant tumors, such as ALCL and HL (37). Due to the targeting effect of antibodies, BV specifically binds to CD30 on the surface of malignant cells and induces cytotoxicity through MMAE-induced cell cycle arrest (38). This ADC combines the targeting selectivity of monoclonal antibodies with the high cytotoxicity of MMAE, achieving high antitumor activity and low toxicity and side effects compared with traditional chemotherapy (39).

BV was approved by the Food and Drug Administration (FDA) in August 2011 for the treatment of patients with sALCL who have experienced failure of first-line multiagent chemotherapy at least once (40). The NCCN guidelines also recommend BV as the preferred option as second-line treatment for R/R patients, regardless of whether a transplant is intended (26). A multicenter study conducted in Italy evaluated the effectiveness of BV in 40 patients with R/R sALCL (18 ALK⁺ and 22 ALK⁻). Of those, 31 (77.5%) achieved a favorable response after a median of four cycles of single-agent BV, with an overall response rate (ORR) of 62.5% (45% CR) (41). In addition to retrospective studies, prospective trials have also confirmed the efficacy of BV in ALCL. A phase 2 study (NCT00866047) showed a CR rate of 66% with an estimated 5-year OS and PFS rate of 60 and 39%, respectively (42). According to the present analysis, BV has good developmental and application prospects, with great potential to be used in the treatment of R/R ALCL.

Although patients with R/R ALCL have a high response rate to BV treatment and a good prognosis, disease progression still occurs in some patients following BV monotherapy-induced remission. The effect of BV retreatment has been explored in previous studies. A prospective study (NCT00947856) involving 8 patients with sALCL reported a ORR of 88%

(63% CR) to BV retreatment and controllable safety (43). A retrospective multicenter study reported similar results (ORR, 70%; CR, 60%) (44). These two studies suggested that BV might be a promising option for the retreatment of patients with R/R ALCL.

Given the side effects and unimproved efficacy of traditional chemotherapy, as well as the excellent results of BV in patients with R/R ALCL, Fanale *et al* (45) evaluated the efficacy of front-line BV in combination with cyclophosphamide, doxorubicin and prednisone (BV + CHP) in untreated patients with primary tumors. The study showed an estimated 5-year PFS and OS rate of 47 and 79%, respectively, and continued CR was maintained in 56% (9/16) of patients with ALCL until the end of the study, which indicated that frontline BV + CHP could yield durable benefits and might be a curative treatment option for some untreated patients with primary tumors. Given these promising results, ECHELON-2 (NCT01777152), a large multicenter phase 3 double-blind randomized trial, was launched to compare the efficacy and safety of BV + CHP and CHOP in 452 untreated patients with CD30⁺ PTCL (70% sALCL) (46). After 6 or 8 cycles of treatment, the CR rate and ORR of the BV + CHP group were superior to those of the CHOP group. In addition, BV + CHP also showed a higher 3-year PFS rate (57.1 vs. 44.4%) and a lower risk of death (hazard ratio, 0.66; P=0.0244). This favorable result prompted the FDA to approve BV for patients with previously untreated sALCL in combination with chemotherapy (47).

The most important adverse event (AE) of BV is peripheral neuropathy (PN), which has an incidence rate of >50%; however, in previous studies, a significant portion of patients showed regression or improvement, and there were no fatal AEs associated with BV during the treatment (42,45,46). Furthermore, ECHELON-2 showed that the incidence and severity of PN were similar between the BV + CHP and CHOP groups (46), which meant that BV may not increase the incidence of PN while still improving the curative effect.

Overall, the efficacy of BV in patients with R/R ALCL is considerable, and its retreatment effect on these patients is also worthy of further study. Compared with traditional chemotherapy, BV + CHP can achieve superior therapeutic outcomes without significantly increasing toxicity and it is emerging as a new treatment option for patients with newly diagnosed ALCL. There are several ongoing trials on BV in ALCL (NCT01909934, NCT03766516 and NCT03947255) (Table V).

Pralatrexate. In addition to BV, other US FDA-approved drugs for patients with R/R PTCL include pralatrexate, romidepsin and belinostat (48). Pralatrexate is a novel targeted folic acid agent that can competitively inhibit dihydrofolate reductase, ultimately leading to DNA replication error and tumor cell apoptosis (49).

In a large phase 2 study, PROPEL, patients with R/R PTCL who received a median of three previous systemic treatments achieved an ORR of 29% [11% CR/unconfirmed CR (CRu), 18% PR] and a median duration of response (DOR) of 10.1 months (50). Based on the relatively good and consistent reactivity, in 2009, pralatrexate became the first drug to be approved by the FDA for patients with R/R PTCL. In an international case-matched control analysis of the PROPEL study,

Table IV. Studies on survival following immunotherapy and targeted therapy in patients with ALCL.

A, BV										
First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %
Bartlett <i>et al</i>	NCT00947856	2014	2	BV	28	8	3	5	0	88 (63)
Broccoli <i>et al</i>	/	2017	/	BV	40	40	18	22	0	62.5 (45)
Pro <i>et al</i>	NCT00866047	2017	2	BV	58	58	16	42	0	86 (66)
Fanale <i>et al</i>	NCT01309789	2018	1	BV + CHP	26	19	3	16	0	100 (92) ^a
Horwitz <i>et al</i>	NCT01777152	2019	3	BV + CHP	226	162	49	113	0	83 (68) ^a
				CHOP	226	154	49	105	0	72 (56) ^a
Fukuhara <i>et al</i>	/	2020	/	BV	28	10	/	/	10	70 (60)
B, Pralatrexate										
First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %
O'Connor <i>et al</i>	NCT00364923	2011	2	Pralatrexate	115	17	/	/	/	29 (11) ^a ; 35 for ALCL
Advani <i>et al</i>	NCT01336933	2016	2	Pralatrexate + CEOP	33	4	/	/	/	70 (52) ^a ; 100 (75) for ALCL
O'Connor <i>et al</i>	/	2018	/	PROPEL group Control group	80 80	13 12	/	/	/	/
										/

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade (Refs.)
Bartlett <i>et al</i>	NCT00947856	2014	2	BV	28	8	3	5	0	88 (63)	Median PFS, 12.9 months	Median OS, not reached	PN, fatigue, arthralgia and anemia (43)
Broccoli <i>et al</i>	/	2017	/	BV	40	40	18	22	0	62.5 (45)	2-year PFS, 39.1%	2-year OS, 56.9%	Neutropenia and PN (41)
Pro <i>et al</i>	NCT00866047	2017	2	BV	58	58	16	42	0	86 (66)	5-year PFS: ALK-, 39%; ALK+, 37%	5-year OS: ALK-, 61%; ALK+, 56%	PN (42)
Fanale <i>et al</i>	NCT01309789	2018	1	BV + CHP	26	19	3	16	0	100 (92) ^a	5-year PFS, 47%	5-year OS, 79%	PN (45)
Horwitz <i>et al</i>	NCT01777152	2019	3	BV + CHP	226	162	49	113	0	83 (68) ^a	Median PFS ^a , 48.2 months; 3-year PFS ^a , 57.1%	Median OS ^a , not reached	Nausea, neutropenia, diarrhea, pyrexia, constipation, PN, anemia and fatigue (46)
				CHOP	226	154	49	105	0	72 (56) ^a	Median PFS ^a , 20.8 months; 3-year PFS ^a , 44.4%	Median OS ^a , not reached	Nausea, neutropenia, diarrhea, fatigue, constipation, PN, alopecia and anemia
Fukuhara <i>et al</i>	/	2020	/	BV	28	10	/	/	10	70 (60)	Median PFS, 5.3 months	Median OS, not mentioned	Alanine aminotransferase increased, neutropenia and PN (44)
B, Pralatrexate													
First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade (Refs.)
O'Connor <i>et al</i>	NCT00364923	2011	2	Pralatrexate	115	17	/	/	/	29 (11) ^a ; 35 for ALCL	Median PFS ^a , 3.5 months	Median OS ^a , 14.5 months	Thrombocytopenia, mucositis, neutropenia and anemia (50)
Advani <i>et al</i>	NCT01336933	2016	2	Pralatrexate + CEOP	33	4	/	/	/	70 (52) ^a ; 100 (75) for ALCL	2-year PFS ^a , 39%	2-year OS ^a , 60%	Anemia, thrombocytopenia, febrile neutropenia, mucositis, sepsis, increased creatinine and liver transaminases (52)
O'Connor <i>et al</i>	/	2018	/	PROPEL group Control group	80 80	13 12	/	/	/	/	/	Median OS ^a , 15.2 months Median OS ^a , 4.07 months	/

Table IV. Continued..

C, HDAC inhibitors

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
Coiffier <i>et al</i>	NCT00426764	2012	2	Romidepsin	130	22	1	21	0	25 (15) ^a ; 24 (19) for ALCL	Median PFS ^a , 4 months	Median OS ^a , 11.3 months	Thrombocytopenia, neutropenia and infections	(53)
Coiffier <i>et al</i>		2014		Extension phase of romidepsin							Median PFS, 20 months for objective responders	Median OS, 30 months for objective responders		(57)
Dupuis <i>et al</i>	NCT01280526	2015	1b/2	Romidepsin + CHOP	37	3	0	3	0	68 (51) ^a	30-month PFS ^a , 41.0%	30-month OS ^a , 70.7%	Neutropenia, thrombocytopenia, anemia and nausea	(58)
O'Connor <i>et al</i>	NCT00865969	2015	2	Belinostat	120	15	2	13	0	25.8 (10.8) ^a ; 13 for ALCL	Median PFS ^a , 1.6 months	Median OS ^a , 7.9 months	Anemia, thrombocytopenia, dyspnea and neutropenia	(54)
Johnston <i>et al</i>	NCT01839097	2021	1	Belinostat + CHOP	23	3	2	1	0	86 (71) ^a at MTD	/	/	Febrile neutropenia, pyrexia, nausea and neutropenia	(59)
Shi <i>et al</i>	/	2015	2	Chidamide	79	17	/	11	/	28 (14) ^a ; 45 for ALK- ALCL	Median PFS ^a , 2.1 months	Median OS ^a , 21.4 months	Thrombocytopenia, leucopenia and neutropenia	(55)
Shi <i>et al</i>	/	2017	2	Chidamide monotherapy	256	35	/	/	/	39.06 ^a	Median PFS ^a , 129 days	Median DOR ^a , 148 days	Thrombocytopenia and neutropenia	(56)
				Chidamide combined with chemotherapy	127					51.18 ^a	Median PFS ^a , 152 days	Median DOR ^a , 169 days	Thrombocytopenia, neutropenia, anemia, and fatigue	
Zhang <i>et al</i>		2021	1b/2	Chidamide + CHOP	128	?				60.2 (40.7) ^a	Median PFS ^a , 10.7 months; 3-year PFS ^a , 32.8%	/	/	(60)

D, ALK inhibitors

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
Mossé <i>et al</i>	NCT00939770	2017	1/2	Crizotinib 165 mg/m ²	6	6	6	0	0	83 (83)	/	/	Neutropenia	(66)
				Crizotinib 280 mg/m ²	20	20	20	0	0	90 (80)	/	/	Neutropenia	
Gambacorti-Passerini <i>et al</i>	NCT01121588	2018	1b	Crizotinib 250 mg twice daily	44	18	18	0	0	52.9 (47.1)	2-year PFS, 63.0%	Median OS, not reached	Nausea, elevated transaminases, vomiting, neutropenia, abdominal pain, leukopenia and fatigue	(67)

Table IV. Continued..

E, Everolimus										
First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %
Witzig <i>et al</i>	NCT00436618	2015	2	Everolimus	16	2	/	/	2	44 ^a
										PFS/EFS
										Median OS ^a , 10.2 months
										Median PFS ^a , 4.1 months
Kim <i>et al</i>	NCT01198665	2016	2	Everolimus + CHOP	30	7	0	7	0	90 (57) ^a
										/
										2-year OS ^a , 70%
										Neutropenia and thrombocytopenia

^aResult is for all enrolled patients, not just ALCL patients. ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ORR, overall response rate; CR, complete remission; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; BV, bentuximab vedotin; PN, peripheral neuropathy; CHOP, cyclophosphamide, vincristine and prednisone; CHP, cyclophosphamide, vincristine, doxorubicin and prednisone; CEOP, cyclophosphamide, etoposide, vincristine and prednisone; DOR, duration of response; MTD, maximum tolerated dose; CHOEP, cyclophosphamide, vincristine, doxorubicin, etoposide and prednisone; HDAC, histone deacetylase.

the median OS time of the PROPEL group was superior to that of the control group (15.24 vs. 4.07 months). In patients with ALCL, the OS curves of the two groups coincided, suggesting that pralatrexate might have a similar efficacy to that of treatment previously used in ALCL (51). The addition of new drugs to conventional cytotoxic drugs has the potential to yield unexpected clinical benefits for patients, such as the aforementioned successful discovery of CHOEP and BV + CHP; for that reason, some clinical centers are experimenting with different drug combinations. Advani *et al* (52) studied the effects of cyclophosphamide, etoposide, vincristine and prednisone alternating with pralatrexate as first-line treatment for patients with PTCL, but the results did not show a higher response rate or more favorable survival compared with the traditional CHOP regimen (NCT01336933).

HDAC inhibitors. Romidepsin, belinostat and chidamide are HDAC inhibitors that act at the epigenetic level to induce tumor cell cycle arrest and apoptosis. Results from three phase II clinical studies showed that among patients with R/R PTCL who had previously received a median of two or three systemic therapies, the ORR was 25% (15% CR), 25.8% (10.8% CR) and 28% (14% CR), and the median DOR was 17, 13.6 and 9.9 months, following treatment with romidepsin (53), belinostat (54) and chidamide (55), respectively. The most common AEs of grade 3 or higher were hematological toxicities (e.g., thrombocytopenia and neutropenia), with the lowest incidence observed following treatment with belinostat. Due to the poor survival of patients with R/R PTCL and the relatively effective and persistent reactivity of romidepsin and belinostat shown in those studies, these drugs were approved by the US FDA. Chidamide, a novel benzoamide-like HDAC inhibitor, was approved by the Chinese FDA in December 2014 for R/R PTCL and is currently only available in China. In a multicenter real-world study, the ORR of chidamide monotherapy was 39% and reached 51% when combined with chemotherapy (56). In addition, a long-term follow-up study of the romidepsin trial showed a median DOR of 28 months for patients who responded to treatment, and a median PFS time of 29 months for those who achieved CR/CRu, and the continuous application of romidepsin did not increase its toxicity (57). Therefore, romidepsin can enable patients to obtain an effective, long-lasting and relatively safe response, laying an important foundation for its further study in patients with PTCL.

The efficacy of these three drugs in combination with conventional chemotherapy in first-line treatment was also studied separately. In the phase 2 trial of romidepsin in combination with CHOP, the ORR was 68% (51% CR), with a 30-month PFS and OS rate of 41.0 and 70.7%, respectively (NCT01280526) (58), indicating that the combination appears to be a feasible option. However, the higher toxicity of the romidepsin group, with grade 3-4 neutropenia in 89% of patients, and at least one serious AE in 68% of patients, should not be ignored. In addition, the existence of cardiotoxicity needs to be determined. An ongoing multicenter phase 3 randomized controlled study (NCT01796002) is currently comparing the efficacy of CHOP with that of romidepsin plus CHOP. In the belinostat combined with CHOP study, the ORR was 86% (71% CR) at the maximum tolerated dose of belinostat, and

Table V. Ongoing trials of ALCL.

Clinical trial ID	Status	Regimen	Phase	Patient diagnosis	Patient number
NCT01909934	Active, not recruiting	BV	4	R/R ALCL	50
NCT04306887	Recruiting	TQ-B3101	2	R/R ALCL	30
NCT03766516	Recruiting	BV	/	R/R ALCL or Classical HL	150
NCT03703050	Recruiting	Nivolumab	2	R/R ALK+ ALCL	38
NCT03443128	Recruiting	Vinorelbine	2	Child and adolescent R/R ALCL	20
NCT03505554	Recruiting	Lorlatinib	2	ALK+ R/R ALCL	12
NCT02419287	Active, not recruiting	Crizotinib	2	ALK+ ALCL resistant or refractory to standard cytotoxic treatment	12
NCT03947255	Recruiting	BV	2	HL, PTCL and ALCL	80
NCT01796002	Active, not recruiting	Romidepsin + CHOP	3	PTCL	421
NCT04526834	Recruiting	Anti-CD30 CAR T cells	1	ALCL, PTCL, DLBCL, Extranodal NK/T-cell Lymphoma and PMBCL	21
NCT04008394	Recruiting	Anti-CD30 CAR T cells	1	Adult TCL, ALCL, AITL, NK/T-cell Lymphoma, PTCL and HL	50
NCT03049449	Recruiting	Anti-CD30 CAR T cells	1	ALCL, EAT-CL, DLBCL, PTCL and Extranodal NK/T-cell Lymphoma	79
NCT04083495	Recruiting	Anti-CD30 CAR T cells	2	PTCL	20
NCT03383965	Recruiting	Anti-CD30 CAR T cells	1	HL and ALCL	20

BV, brentuximab vedotin; R/R, relapsed or refractory; ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; TCL, T-cell lymphoma; EAT-CL, Enteropathy-associated T-cell lymphoma; ALK+, anaplastic lymphoma kinase-positive; HL, Hodgkin's lymphoma; PTCL, peripheral T-cell lymphoma; CAR, chimeric antigen receptor; CHOP, cyclophosphamide, vincristine, doxorubicin and prednisone; PMBCL, Primary Mediastinal Large B-Cell Lymphoma.

the incidence of AEs was similar to that following treatment with belinostat alone, suggesting that the combination would not cause additional toxicity (59). Chidamide, when combined with the CHOEP regimen, had an ORR of 60.2% (40.7% CR) and a 3-year PFS rate of 32.8% in 113 newly diagnosed PTCL patients who received 20 mg chidamide twice a week. The AEs were also at a controllable level (60).

However, all of these studies were non-randomized, single-arm trials, with a small patient population and without a separate analysis of the basic characteristics and survival outcomes of the patients with ALCL. Therefore, the efficacy of these drugs in ALCL needs to be further confirmed. At present, the drugs can be considered for patients who are R/R and have no response to treatment with BV; however, their role in combination with chemotherapy in first-line treatment needs to be further studied.

ALK inhibitors. ALK is a tyrosine kinase receptor that belongs to the insulin receptor superfamily. Under normal circumstances, the expression of ALK is limited to neurogenic cells in humans, while the translocation of the ALK chromosome leads to its expression and continuous activation. The expression of ALK can be found in ALK⁺ ALCL, inflammatory myofibroblastoma and non-small cell lung cancer (NSCLC). Fusions of ALK have a clear carcinogenic potential, since their abnormal tyrosine kinase activity can promote cell proliferation and survival (61-63). The carcinogenic effect of ALK is mediated by triggering a large number of downstream molecules of the intracellular signaling cascade. Therefore, ALK can be used as an ideal therapeutic target for ALK⁺ disease. At present, there are three generations of ALK inhibitors; the first generation is crizotinib, the second generation contains seritinib, alitinib and brigatinib, and the third generation is lorlatinib (64). In 2011, crizotinib was approved by the FDA for the treatment of patients with ALK⁺ NSCLC (40); it has also been tried out in patients with ALCL and ALK⁺ mutations in recent years and a series of clinical trials are underway.

Gambacorti Passerini *et al* (65) reported an ORR of 90.9% (10/11 cases) in R/R ALK⁺ lymphoma following crizotinib treatment. Among the 9 patients with CR, 4 obtained continuous CR following long-term treatment with crizotinib, 2 experienced progression following CR, and 3 received allo-HSCT and remained in CR.

The efficacy and safety of crizotinib in patients with advanced or R/R ALCL have also been demonstrated in two clinical trials (66,67). One enrolled 26 patients with ALK⁺ ALCL, aged 1-21 years, who received 280 or 165 mg/m² crizotinib twice daily and had an ORR of 88% (CR 81%) (66). The positive results led to the FDA approval of crizotinib for use in children aged ≥1 years old or young adults with R/R ALK⁺ ALCL in 2021 (68). Another study showed that in 18 patients with R/R ALCL, ORR and CR were 52.9 and 47.1%, respectively, with a median DOR of 2.6 years (67). Although 88.6% of the patients experienced AEs, most were grade 1 and there were no fatal AEs.

Several case reports also reported that crizotinib alone or combined with HSCT had a good therapeutic effect in R/R ALCL (69-74). Alitinib, a second-generation ALK inhibitor, has also been reported to induce CR in patients with ALK⁺ ALCL (75). All these studies suggested that ALK inhibitors could improve the prognosis of patients with ALK⁺ ALCL, but there is also a report of rapid recurrence following the withdrawal of crizotinib (76); therefore, long-term follow-ups are still required to evaluate the efficacy and safety of these drugs.

Patients with R/R ALCL usually have a poor prognosis, and there is no consensus on the treatment that should be administered to these patients. Although research and clinical practice have confirmed that BV has a favorable effect on patients with R/R ALCL, its long-term AEs, such as PN, cannot be ignored. In recent studies, crizotinib has been shown to have significant and durable antitumor effects and a good tolerance in patients with R/R ALCL, which suggests its potential as a treatment option. However, it can only be used in ALK⁺ patients and is currently only tentatively used in R/R patients. The matter of

recurrence following drug withdrawal, and whether crizotinib can be used as first-line treatment, require further study.

Platelet-derived growth factor receptor (PDGFR) inhibitors. Even following BV treatment or HSCT, the prognosis of patients with R/R ALCL has been reported to remain poor (77); for that reason, novel drugs have gradually started to be used for the treatment of these patients. In addition to the BV, pralatrexate, HDAC inhibitors and ALK inhibitors aforementioned, other emerging therapies, such as PD-1/PD-L1 inhibitors, PDGFRB inhibitors and other NPM-ALK fusion protein inhibitors, have also been widely studied and found to have potential benefits. The signal transduction pathways, immunotherapies and targeted therapies in ALCL are illustrated in Fig. 1.

PDGF is a peptide regulatory factor that stimulates tissue cell growth and plays a biological role by phosphorylating and activating PDGFR and initiating the PDGF/PDGFR signaling pathway. ALK can induce the expression of JunB and JUN through the PI3K/Akt/mTOR signaling pathways (78,79), and then bind to and activate the PDGFRB promoter. The expression and activation of PDGFR is a key event in lymphoma cell survival and proliferation. A previous study (80) showed that the therapeutic inhibition of PDGFR significantly prolonged the survival time of NPM-ALK transgenic mice. The study also reported the case of a 27-year-old patient with stage III ALK⁺ ALCL, who was unresponsive to conventional chemotherapy and relapsed following ASCT (80). After 10 days of treatment with 400 mg/day imatinib, a kind of PDGFR inhibitor, the tumor marker levels decreased and the patient rapidly achieved CR, which was maintained for 22 months. A follow-up study showed that there was no recurrence 1 year after the withdrawal of imatinib (81). These results suggested that PDGFR inhibitors may be an effective treatment for NPM-ALK⁺ ALCL. In addition, PDGFRs exist not only in NPM-ALK⁺ TCL but also in ALK⁻ ALCL. Therefore, the application of PDGFR inhibitors is worthy of further study not only in patients with ALK⁺ ALCL but also in those with ALK⁻ ALCL.

mTOR inhibitors. Most ALK⁺ ALCL exhibit t(2;5)(p23;q35) translocation and mediate the expression of the NPM-ALK fusion protein. This fusion protein and its associated signaling pathways, such as the PI3K/Akt, JAK/STAT and RAS/MEK/ERK pathways, are potential targets for ALCL therapy (82-88). mTOR is an important downstream protein kinase of the PI3K-Akt and MEK/ERK signaling transduction pathways (89,90); it can accelerate the synthesis of intracellular proteins and provide the material basis for the growth of tumor cells. mTOR can be detected in 80% of patients with ALCL and is associated with the expression of ALK (91,92). mTOR inhibition can decrease the phosphorylation of mTOR and induce cell cycle arrest and apoptosis (93).

Everolimus is such an mTOR inhibitor (90). A phase II trial evaluating the efficacy of everolimus in patients with R/R TCL reported an ORR of 44% (PR in 1/2 patients with ALCL), with a median PFS and OS time of 4.1 and 10.2 months, respectively, following treatment with 10 mg everolimus daily (94). This indicated that everolimus had an antitumor effect in patients with TCL. Another phase II study of everolimus

combined with CHOP as first-line treatment for patients with PTCL reported an ORR of 90% (27/30 cases; CR 57%). A total of 29% (2/7) of patients with ALK⁻ ALCL achieved CR (ALK⁺ patients were not included in this study). However, the response duration was relatively short, suggesting that the value of this combination may be limited (95). A previous study reported the successful application of rapamycin (an mTOR inhibitor) in a patient with cutaneous ALCL (96). In the case of a 70-year-old woman who was unresponsive to treatment with a rituximab, etoposide, methylprednisolone, Adriamycin, cyclophosphamide and cisplatin regimen, a rituximab, etoposide, methylprednisolone, cytosine arabinoside and cisplatin regimen, or SGN-30, the tumor growth was halted following the use of rapamycin combined with local radiation for <6 weeks, and the patient had been taking rapamycin for 18 months and maintained a continuous CR.

In addition, studies have shown that the combination of alectinib and everolimus (97) or the combination of crizotinib and everolimus (98) can have a synergistic effect on the growth of ALK⁺ ALCL cells, indicating that the combination of ALK inhibitors and mTOR inhibitors is worthy of further clinical investigation.

PD-1/PD-L1 inhibitors. PD-1 is a receptor protein on the surface of activated T cells and a member of the immunoglobulin superfamily. PD-L1 protein is the ligand of PD-1 and is expressed in a variety of tumor cells. The combination of the two proteins transmits a negative regulatory signal to T cells, inhibits T-cell activation, proliferation and cytokine production, induces T-cell apoptosis and enables the immune escape of tumor cells (99-101). The FDA has approved PD-1/PD-L1 inhibitors for the treatment of lung cancer, Hodgkin's lymphoma and other tumors (102-104).

The association between NPM-ALK and PD-L1 was recently clarified (105-107). The signalosome containing growth factor receptor-bound protein 2 (GRB2)/SOS Ras/Rac guanine nucleotide exchange factor 1 (SOS1) and STAT3 can induce the expression of PD-L1, in which GRB2/SOS1 plays a role by activating the MEK-ERK and PI3K-Akt signaling pathways (106). These signaling networks induce the expression of PD-L1 through the action of the transcription factors interferon regulatory factor 4 and basic leucine zipper ATF-like transcription factor 3 on the PD-L1 gene (106). In addition, targeting the carcinogenic signaling pathway in ALK⁺ ALCL could suppress the PD-L1-mediated ability of tumor immune escape (106).

Shen *et al* (108) examined the expression of PD-L1 in 95 patients with ALCL and found that PD-L1 expression was higher in ALK⁺ ALCL than that in ALK⁻ ALCL (76 vs. 42%; $P=0.002$), but that there was no difference in OS between patients with PD-L1⁺ ALCL and those with PD-L1⁻ ALCL ($P=0.44$). This suggested that the prognostic predicting ability of PD-L1 expression for ALCL was not significant, but this is an area that requires further research (107). Kong *et al* (109) deemed that being PD-L1⁺ is associated with a poor prognosis in ALK⁻ ALCL. Among 44 patients with ALK⁻ ALCL, patients with PD-L1⁺ had an inferior median survival time (38 vs. 262 months; $P=0.03$); Kong *et al* (109) analyzed the reasons for this phenomenon and concluded that it may have been due to the difference in the PD-L1 positivity rate between

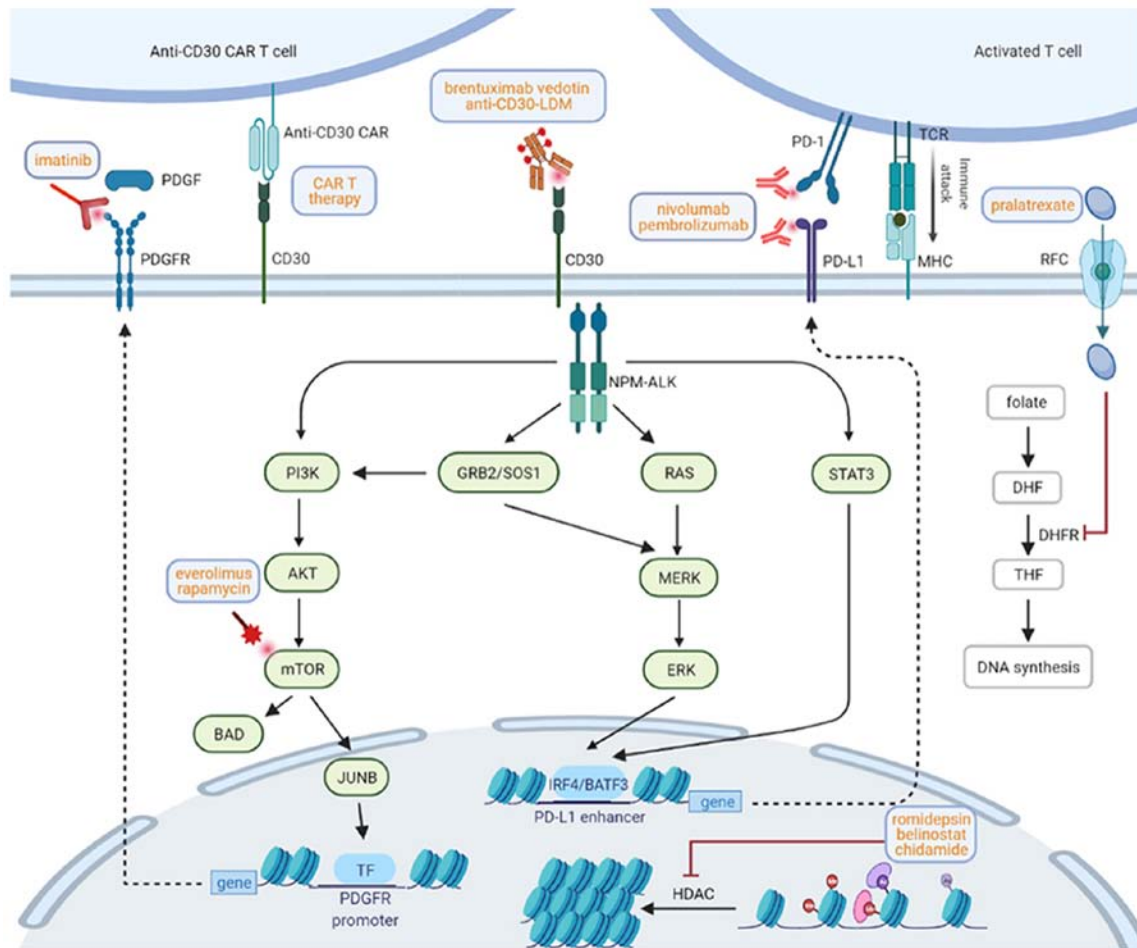


Figure 1. Signal transduction pathways, immunotherapies and targeted therapies in anaplastic large cell lymphoma. PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; CAR, chimeric antigen receptor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; MHC, major histocompatibility complex; RFC, reduced folate carrier; DHF, dihydrofolate; DHFR, dihydrofolate reductase; THF, tetrahydrofolate; HDAC, histone deacetylase; NPM-ALK, nucleophosmin-anaplastic lymphoma kinase; mTOR, mammalian target of rapamycin; TF, transcription factor; Grb2, growth factor receptor-bound protein 2; SOS1, SOS Ras/Rac guanine nucleotide exchange factor 1; IRF4, interferon regulatory factor 4; BATF3, basic leucine zipper ATF-like transcription factor 3; ADC, antibody-drug conjugate; LDM, lidamycin; TCR, T cell receptor; BAD, B-cell lymphoma 2-associated death promoter; JUNB, recombinant Jun B Proto Oncogene.

the two studies and the more aggressive disease experienced by patients in the previous study by Shen *et al* (108).

These studies provide a theoretical basis for the application of PD-1/PD-L1 inhibitors in R/R ALCL. In two previous case reports, 2 patients with ALK⁺ ALCL who relapsed after chemotherapy and ALK inhibitor treatment (one of whom also underwent allo-HSCT) obtained a sustained CR following treatment with nivolumab (3 mg/kg/2 weeks) (110,111). Another patient (112) with stage IV ALK⁺ ALCL who experienced relapse following chemotherapy, ASCT, allo-HSCT and BV treatment, was administered pembrolizumab (2 mg/kg; 1 dose of each at weeks 1 and 6, then once every 3 weeks) and obtained a CR after the third dose. These reports provide a clinical basis for the application of anti-PD1/PD-L1 therapy in R/R ALCL. A clinical trial (NCT03703050) evaluating the response of patients with progressive R/R ALK⁺ ALCL to nivolumab or its use as consolidative therapy in patients with a CR after relapse is currently recruiting.

Chimeric antigen receptor T cells (CAR-T) therapy. As a major breakthrough in immunology, the emergence of CAR-T

therapy has significant implications for the treatment of R/R B-cell NHL (113,114). However, its development in T-cell malignancies is fraught with difficulties and challenges, due to targetable antigens, cell fratricide and other issues (115). The presence of CAR-T cells that could recognize CD30 offers hope for patients with ALCL. As previously described, CD30 is widely expressed in ALCL cells. Several clinical trials on the efficacy, safety or optimum dose of CD30 CAR-T therapy in patients with R/R CD30⁺ lymphocyte malignancies (including ALCL) are ongoing (NCT04526834, NCT04008394, NCT03049449, NCT04083495 and NCT03383965) (Table V).

Others. The MYC proto-oncogene, basic helix-loop-helix transcription factor gene family and its products can promote cell proliferation, differentiation and transformation, and play an important role in a variety of tumors, while ALCL can induce the expression of MYC protein in several ways (116,117). In addition, MYC can regulate antitumor immunity by controlling the expression of PD-L1 in ALCL (118,119). The inhibition of MYC had a toxic effect on the DEL ALK⁺ ALCL cell line,

suggesting that use of the MYC inhibitor may be an effective breakthrough in the treatment of ALCL in the future (117).

Lidamycin (LDM) is a highly effective enadyne antitumor antibiotic that kills tumor cells by directly acting on DNA chains to cause DNA damage (120). The LDM molecule is composed of an apoprotein and highly active enadyne chromophore (121). Anti-CD30-LDM, obtained by coupling LDP with CD30 by genetic engineering, is a new type of ADC that has exhibited strong tumor-targeting and antitumor effects in CD30⁺ ALCL cells and a Karpas299 mouse model, with no obvious toxicity to normal tissue (122). Further experiments showed that the combination of crizotinib and anti-CD30-LDM had a significant synergistic inhibitory effect on ALK⁺ ALCL cells *in vitro* and *in vivo* (123).

Other agents, such as KRCA-0008 (a co-inhibitor of wild-type ALK and crizotinib-resistant ALK mutant) (124), ZYY (a novel ALK inhibitor) (125) and tyrosine kinase 2 (a member of the JAK family of tyrosine kinases) (126) inhibitors, have been studied in ALCL and achieved good responses in a series of *in vivo* and *in vitro* trials, providing new options for the treatment of ALCL and the potential to improve patient prognosis.

5. Conclusions

ALCL is a type of lymphoma with a low incidence, which makes carrying out clinical research challenging. Traditional chemotherapy, such as the CHOP regimen, is still recommended for the first-line treatment of ALCL due to its acceptable AEs and relatively satisfactory treatment effects and survival rate compared with intensive chemotherapy. HSCT can be administered to certain patients and improve their survival, but the increased AEs and TRM cannot be ignored, particularly with regard to allo-HSCT. Targeted therapy and immunotherapy, such as ALK inhibitors, HDAC inhibitors, and BV, have exhibited high response rates and favorable survival rates for patients with ALK⁺ or CD30⁺ R/R ALCL, but their application as first-line therapy requires further exploration. In addition, other novel drugs, such as mTOR inhibitors, PDGFR inhibitors and PD-1/PD-L1 inhibitors, have been proven to be effective in certain case reports, offering options for R/R patients. However, the relatively high price is an important reason to limit the widespread application of immunotherapy. In addition, how to evaluate and determine which immunotherapy regimen to use and how to predict its effectiveness, as well as the AEs and drug resistance of immunotherapy, all need further research.

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Authors' contributions

XS wrote the manuscript, XF provided the main outline and direction of the manuscript, and helped to revise the content of the manuscript. DL and YL summarized the data and tables, and helped to revise the manuscript. XW provided the latest ideas and polished the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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