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Review

Advances and challenges of immunotherapies in NK/T cell lymphomas

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SUMMARY

Natural killer (NK)/T cell lymphoma (NKTCL) is a rare subtype of Epstein-Barr virus (EBV)-associated non-Hodgkin lymphoma characterized by poor clinical outcomes. It is more common in East Asian and Latin American countries. Despite the introduction of asparaginase/pegaspargase-based chemotherapy, the prognosis of patients with advanced NKTCL needs to be improved, and few salvage treatment options are available for relapsed/refractory patients who fail chemotherapy. Although many unknowns remain, novel treatment strategies to further improve outcomes are urgently needed. Immunotherapy has emerged and shown favorable antitumor activity in NKTCL, including monoclonal antibodies targeting immune checkpoint inhibitors, other receptors on the cellular membrane, and cellular immunotherapy, which could enhance immune cells attack on tumor cells. In this review, we provide an overview of recent immunotherapy in NKTCL, focusing on programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), chimeric antigen receptor (CAR) T cells, EBV-specific cytotoxic T lymphocytes, immunomodulatory agents, and other targeted agents, as well as the current progress and challenges in the field.

INTRODUCTION

Natural killer/T cell lymphoma (NKTCL) is a rare and highly aggressive subtype of non-Hodgkin lymphoma (NHL) with a strong association with Epstein-Barr virus (EBV) infection.[1–3] It is characterized by the malignant proliferation of mature NK/T cells and extranodal involvement, leading to distinct features such as prominent necrosis, vascular damage, and a cytotoxic phenotype.[3,4] The incidence of NKTCL varies substantially by region, accounting for less than 1% in Western countries but exceeding 10% in Latin America and East Asia.[5–7] The molecular pathogenic pathways and deregulated genes in EBV-associated NKTCL are mainly summarized in Figure 1.[8–10]

Anthracycline regimens are largely ineffective for NKTCL due to overexpression of the multidrug resistance gene and its related P-glycoprotein (P-gp); therefore, asparaginase or pegaspargase-based regimens have been introduced as the primary treatment for NKTCL.[11–15] At present, P-GEMOX, DDGP, SMILE, VIPD, and MESA regimens have shown high efficacy in treating early-stage NKTCL (Figure 2).[16–22] Unfortunately, even with asparaginase regimens, the prognosis for patients with advanced disease remains bleak, with a 5-year overall survival (OS) rate of approximately 15%–25%.[23–26] More than 10% of patients with NKTCL show primary resistance to asparaginase chemotherapy.[27] The prognosis is even worse for relapsed/refractory (r/r) disease, and the available salvage therapies are limited. Therefore, a novel therapeutic strategy is needed to treat patients with NKTCL. Immunotherapy is emerging as a potential approach for advanced or r/r NKTCL and has demonstrated promising clinical efficacy.

In this review, we described the available immunotherapy options for patients with NKTCL focusing on immune checkpoint inhibitors (ICIs), including anti-programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) antibodies, anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibodies, and other monoclonal antibodies (mAbs) related to regulating immune function (brentuximab vedotin, daratumumab, alemtuzumab, and mogamulizumab). We also describe the current knowledge about cellular immunotherapeutic approaches involving antigen-specific EBV-cytotoxic T lymphocytes (EBV-CTLs) and chimeric antigen receptor (CAR)-T cells therapy (Table 1). Moreover, immunomodulatory agents are described in the section. A schematic representation of immunotherapy targets for NKTCL is depicted in Figure 3.

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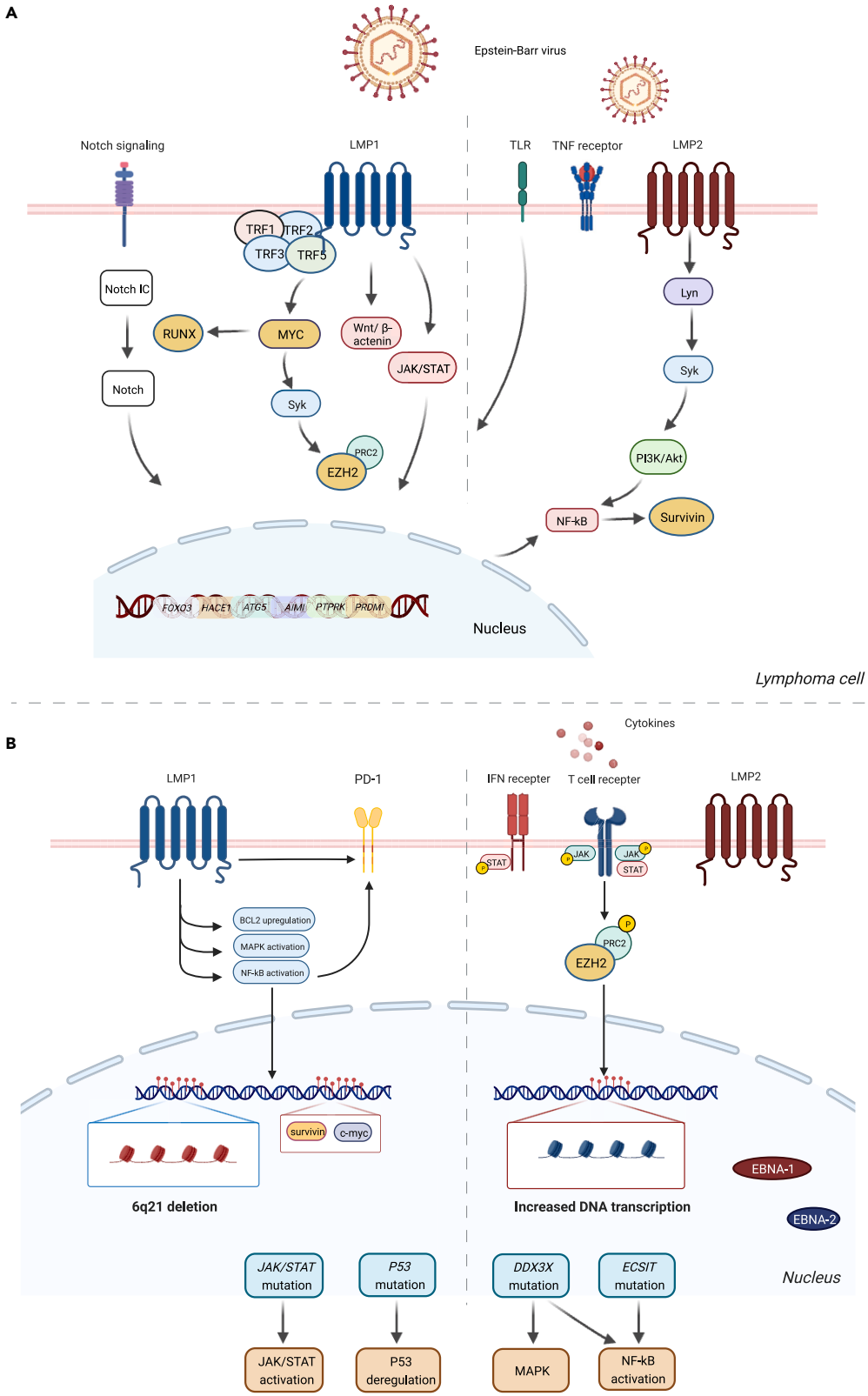
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Epstein-Barr virus
Notch signaling
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TLR
TNF receptor
LMP2
TRF1
TRF2
TRF3
TRF5
Notch IC
RUNX
MYC
Wnt/ β-actenin
JAK/STAT
Notch
Syk
PRC2
EZH2
Lyn
Syk
PI3K/Akt
NF-kB
Survivin
FOXO3
HACE1
ATG5
AIM1
PTPRK
PRDM1
Nucleus
Lymphoma cell
B
Cytokines
LMP1
PD-1
IFN recepter
T cell recepter
LMP2
STAT
JAK
JAK
STAT
BCL2 upregulation
MAPK activation
NF-kB activation
PRC2
EZH2
survivin
c-myc
6q21 deletion
Increased DNA transcription
EBNA-1
EBNA-2
Nucleus
JAK/STAT mutation
P53 mutation
DDX3X mutation
ECSIT mutation
JAK/STAT activation
P53 deregulation
MAPK
NF-kB activation

Figure 1. Molecular pathogenic pathways and deregulated genes in Epstein-Barr virus associated NK/T cell lymphoma

Summary of the deregulated genes and key signaling pathways involved in the pathogenesis of Epstein-Barr virus (EBV)-related NK/T-cell lymphoma (NKTL), nasal type, that promote proliferation and survival of the lymphoma cells (A). This figure summarizes the pathogenic molecular mechanisms that are involved in activating JAK/STAT and NF-κB pathways, as well as alterations in deregulated genes, epigenetic dysregulation, and mechanisms of immune evasion (B).

MONOCLONAL ANTIBODY IMMUNOTHERAPY

Checkpoint inhibitors

New treatment approaches, such as ICIs, have demonstrated remarkable antitumor potential in several types of hematopoietic malignancies. Currently, an increasing number of trials of these drugs in lymphomas are underway. PD-1/PD-L1 and CTLA4 are negative regulators of T cell activation that may be potent therapeutic targets in NKTCL.[54]

Antibodies targeting programmed cell death-1/programmed cell death-ligand 1

PD-1 is a coinhibitory molecule that is critical to cancer cells escaping from immune surveillance. PD-L1, the ligand of PD-1, is universally up-regulated in NKTCL by EBV-driven latent membrane protein 1 (LMP1). It triggers NF-κB and MAPK signaling pathways making anti-PD-1/PD-L1 axis a potent immunotherapy target.[33,55,56] Evidence has shown that serum PD-L1 levels are associated with the prognosis of patients with NKTCL. Elevated baseline sPD-L1 levels were associated with an increased risk of worse OS and PFS.[33,57] Recently, randomized clinical trials (RCTs) suggested that blocking the PD-1/PD-L1 axis is a safe and robust treatment for NKTCL, specifically showing potent activity in r/r disease.[58,59]

Pembrolizumab, a humanized anti-PD-1 IgG4 monoclonal antibody, exhibited favorable antitumor effects in seven patients with r/r NKTCL who had failed l-asparaginase-based regimens. The results suggested that the objective response rate (ORR) and complete remission (CR) rate were 100% and 71.4%, respectively. Regarding the treatment-related adverse events (TRAEs), only one patient had grade 2 skin graft-versus-host disease (GVHD).[59] Similarly, two other studies utilizing pembrolizumab and nivolumab showed that these treatments were highly efficacious and well tolerated in patients with r/r NKTCL.[28,29] In preclinical studies, sintilimab demonstrated superior antitumor activity compared to pembrolizumab or nivolumab.[60] A multicenter, single-arm, phase 2 clinical trial, including 28 patients with r/r NKTCL, was designed to provide data on the clinical efficacy and safety of sintilimab. The results of the study illustrated that the ORR was 75.0%, 6 (21.4%) patients achieved CR, and 15 (53.6%) patients achieved PR. The 2-year OS rate was 78.6%, and grade 1-2 decreased lymphocyte count was the most common TRAE.[58] Targeting PD-L1 also produced active antitumor efficacy. Avelumab is a human IgG1 mAb targeting PD-L1 that can enhance antibody-dependent cell-mediated cytotoxicity (ADCC). Kim et al. evaluated the efficacy and safety of avelumab in 21 patients with r/r NKTCL. The phase II study revealed that avelumab was active with an ORR of 38%, a CR rate of 24%, and no grade 4 adverse events occurred.[61] Moreover, the efficacy of the anti-PD-L1 mAb sugemalimab in r/r NKTCL has also been revealed, which induces a high CR rate and durable response without significant toxicity. The results from the GEMSTONE-201 trial (NCT03595657) showed that in 80 eligible patients who received sugemalimab and were followed for a median of 18.7 months, the independent radiologic review committee-assessed ORR was 44.9%. Among them, 28 patients (35.9%) achieved a CR, and seven (9.0%) achieved a PR, with a 12-month duration of response rate of 82.5%. The most treatment-emergent adverse events were grade 1–2 in severity.[34,62]

Combining anti-PD1/PD-L1 antibodies with other innovative treatments, such as the combination of sintilimab and chidamide (a histone deacetylase inhibitor, HDACi), has demonstrated improved antitumor efficacy and safety in r/r NKTCL. A phase Ib/II study involving 45 patients with r/r NKTCL revealed encouraging outcomes, with an ORR of 58.3% (21 out of 36) and a CR rate of 44.4% (16 out of 36) among the evaluated subjects.[63] Sun et al. conducted a retrospective study that assessed the efficacy and safety of combining anti-PD-1 antibodies (pembrolizumab/nivolumab/sintilimab) with anlotinib (small molecule tyrosine kinase inhibitor targeting VEGFR and other tyrosine kinase-mediated pathways), pegaspargase, and radiotherapy in eight patients with localized NKTCL. The results indicated that the 3-year OS and PFS rates of the combined regimen both were 100% (median follow-up, 35.5 months). There were no severe (grade 3/4) hematological toxicities reported.[64]

Overall, PD-1/PD-L1 axis blockade has demonstrated promising antitumor activity as a single agent or in combination in treating NKTCL.[31,65,66] Evidence suggests that anti-PD-1/PD-L1 therapies might also work synergistically with cellular therapies or other therapeutic strategies. Combination regimens through variant antitumor mechanisms may improve the prognosis. Multiple clinical trials are currently underway, investigating therapies such as anti-PD1/PD-L1 inhibitors plus radiotherapy, antiangiogenesis treatment, anti-CD20 (rituximab), anti-CD30 (brentuximab vedotin), or CAR-T cells. Nonetheless, immunotherapy-related adverse events remain a major challenge, especially in the skin, gastrointestinal system, endocrine system, and liver.[67] Trials seeking predictive biomarkers for identifying suitable patients are warranted to improve the response to checkpoint inhibitor-based immunotherapy. Table 2 summarizes the clinical trials of immune-related monoclonal antibodies in NKTCL.

Antibodies targeting cytotoxic T-lymphocyte antigen 4

Cytotoxic T-lymphocyte antigen 4 (CTLA-4/CD152) is a transmembrane T cell inhibitory molecule that binds to B7 ligand expressed on antigen-presenting cells (APCs), triggering T cell anergy and negatively regulating the immune response.[68] Ipilimumab, an anti-CTLA-4 monoclonal antibody, has demonstrated positive therapeutic outcomes in multiple malignancies, including malignant melanoma, lung cancer, and renal cancer.[69–71] To date, a phase I/II clinical trial of patients with non-Hodgkin lymphoma, colorectal cancer, and recurrent melanoma (including NKTCL) was conducted to assess the safety of ipilimumab (NCT01769222). Although clinical data concerning anti-CTLA-4

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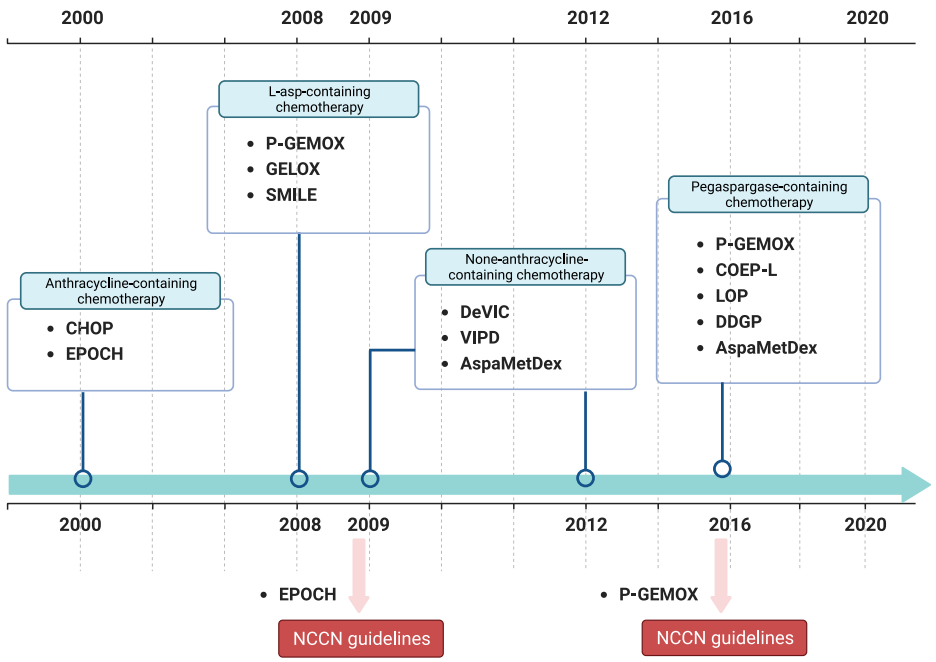
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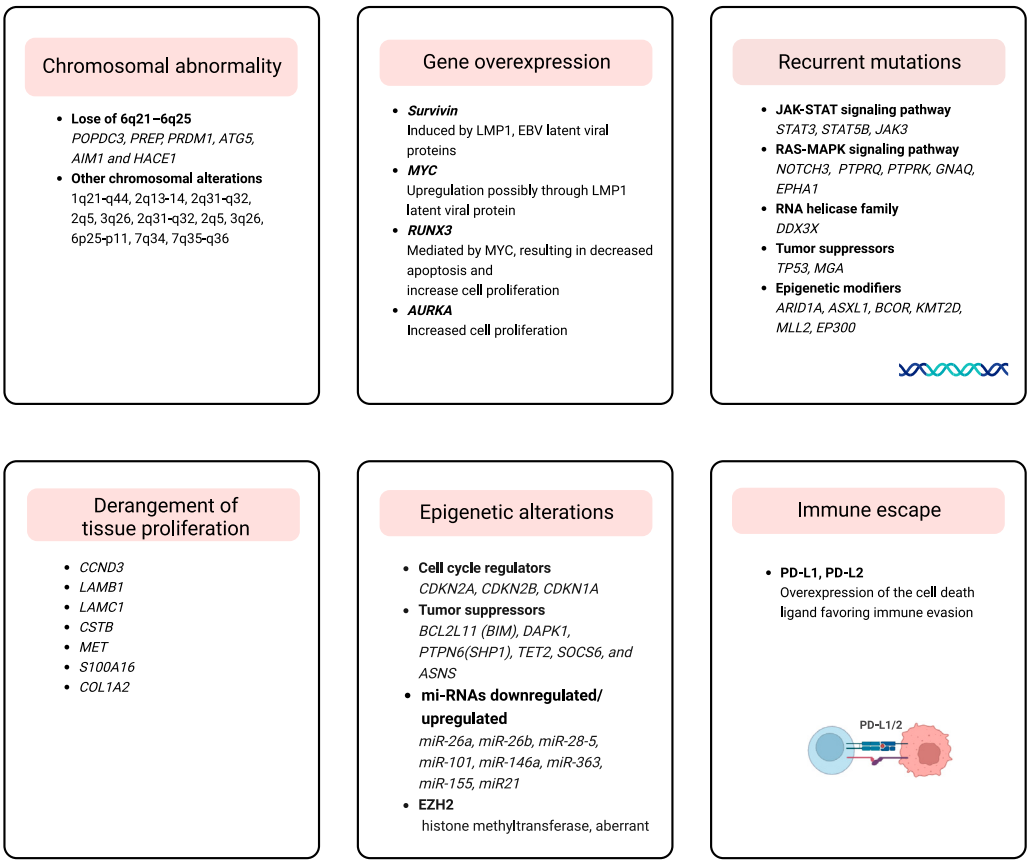
Chromosomal abnormality
Lose of 6q21–6q25
POPDC3, PREP, PRDM1, ATG5, AIM1 and HACE1
Other chromosomal alterations
1q21-q44, 2q13-14, 2q31-q32, 2q5, 3q26, 2q31-q32, 2q5, 3q26, 6p25-p11, 7q34, 7q35-q36
Gene overexpression
Survivin
Induced by LMP1, EBV latent viral proteins
MYC
Upregulation possibly through LMP1 latent viral protein
RUNX3
Mediated by MYC, resulting in decreased apoptosis and increase cell proliferation
AURKA
Increased cell proliferation
Recurrent mutations
JAK-STAT signaling pathway
STAT3, STAT5B, JAK3
RAS-MAPK signaling pathway
NOTCH3, PTPRQ, PTPRK, GNAQ, EPHA1
RNA helicase family
DDX3X
Tumor suppressors
TP53, MGA
Epigenetic modifiers
ARID1A, ASXL1, BCOR, KMT2D, MLL2, EP300
Derangement of tissue proliferation
CCND3
LAMB1
LAMC1
CSTB
MET
S100A16
COL1A2
Epigenetic alterations
Cell cycle regulators
CDKN2A, CDKN2B, CDKN1A
Tumor suppressors
BCL2L11 (BIM), DAPK1, PTPN6(SHP1), TET2, SOCS6, and ASNS
mi-RNAs downregulated/upregulated
miR-26a, miR-26b, miR-28-5, miR-101, miR-146a, miR-363, miR-155, miR21
EZH2
histone methyltransferase, aberrant
Immune escape
PD-L1, PD-L2
Overexpression of the cell death ligand favoring immune evasion
PD-L1/2

Figure 2. Milestones of chemotherapy and main genetic alterations in NKTCL

Timeline of the significant advancements in chemotherapy for managing NKTCL (A). Main genetic alterations in NKTCL (B). *Abbreviations*: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; P-GEMOX, pegaspargase, gemcitabine and oxaliplatin; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide; AspaMetDex, L-asparaginase, methotrexate and dexamethasone; DDGP, dexamethasone, cisplatin, gemcitabine and pegaspargase; COEP-L, cyclophosphamide, vincristine, etoposide, prednisone and L-asparaginase.

monoclonal antibodies for NKTCL treatment are largely limited, CTLA-4 inhibitors may show promise. More evidence from preclinical and clinical studies is still needed to further explore the use of CTLA-4 inhibitors in treating hematological malignancies.

Targeting surface antigens

Novel monoclonal antibody-based therapies have emerged as essential strategies in NKTCL treatment. Monoclonal antibodies exert their effects primarily through ADCC, complement-dependent cytotoxicity, and apoptosis induction. Numerous ongoing clinical trials are dedicated to exploring monoclonal antibodies, either as standalone agents or in combination with other therapies, to enhance efficacy against NKTCL.

Anti-CD25 (IL-2Rα) monoclonal antibody

CD25, also known as IL-2Rα, is a subunit of the interleukin-2 receptor and plays a significant role in regulating the immune response. It is mainly expressed on the surface of the effector T cells, regulatory T cells (Tregs), Langerhans cells, and B cells, exerting proinflammatory effects.[72,73] CD25 overexpression was induced by EBV-driven LMP1 in NKTCL through the activation of the NF-κB and MAPK pathways.[74] Expression of CD25 was detected in 33.0%–53.8% of patients with NKTCL and was significantly correlated with B symptoms and elevated serum lactate dehydrogenase.[40,75] The high-level serum soluble form of IL-2Rα (sIL-2Rα) was elevated and correlated with poor prognosis in various hematologic malignancies and solid tumors.[76–78] The serum CD25 levels were elevated in NKTCL, especially in patients with hemophagocytic syndrome (HPS) or B symptoms. Data from preclinical and clinical studies suggest that CD25 may be a potential therapeutic target for $CD25^+$ NKTCL. High sIL-2Rα level was significantly correlated with poor treatment response and survival for patients with NKTCL.[40] In a case report, a patient with steroid dependent hemophagocytic syndrome was treated with daclizumab (anti-CD25 antibody), allowing successful withdrawal of corticosteroid therapy.[79] Basiliximab, a recombinant chimeric mAb that specifically binds CD25 on the surface of activated T-lymphocytes, is an immunosuppressive agent. ^{131}Iodine-labeled Basiliximab has shown promise in an early phase I trial, demonstrating CR or PR in patients with $CD25^+$ lymphoma.[80] A phase II trial is currently underway to evaluate the efficacy and safety of basiliximab with pegaspargase in patients with r/r NKTCL (NCT04337593).

Anti-CD56 monoclonal antibody

CD56 (neural cell adhesion molecule 1), a 200–220 kDa cell surface glycoprotein, is expressed highly in 76.1%–90% of NKTCL.[81–84] IMGN901 (huN901-DM1) is an anti-CD56 mAb with high affinity binding to CD56. IMGN901 has shown safety and promising efficacy in CD56-positive malignancy in a phase I/II study.[85] Ishitsuka et al. found that IMGN901 demonstrated a selective affinity for the NK-92 MI, a CD56-positive NK cell line. The antibody significantly inhibited the cells from growing when it bound to membrane CD56.[50] Targeting CD56 with IMGN901 represents a potential therapeutic modality against NKTCL. Therefore, anti-CD56-based therapies, either as monotherapy or in combination, warrant further investigation on a larger scale in this patient population.

Anti-CD30 monoclonal antibody

CD30 (TNFRSF8) is a multifunctional transmembrane protein within the tumor necrosis factor receptor (TNFR) superfamily. It exhibits high expression on activated T- and B lymphocytes, as well as certain NHL cells. CD30 has been reported to stimulate T cells to promote the production of cytokines that include IL-2, IFN-γ, and TNF.[86] Approximately 70% of patients with NKTCL exhibit CD30 overexpression, making it an ideal target for NKTCL immunotherapy.[87] Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) combining CD30 mAb with the microtubule inhibitor monomethyl auristatin E (MMAE), which has been approved by the FDA for patients with $CD30^+$ lymphoproliferative disorders, such as cutaneous anaplastic large cell lymphoma, peripheral T cell lymphomas, and mycosis fungoides. As mentioned earlier, CD30 is also proposed as a potential therapeutic target for NKTCL because of its high expression. In a later multicenter, open-labeled phase II trial study, data from 33 patients with r/r $CD30^+$ NHL (including 7 subjects with NKTCL) who were treated with single-agent BV (1.8 mg/kg) were reported. Among this cohort, the ORR for NKTCL was 29%, with one case achieving CR and another obtaining PR, and the response lasted for more than one year.[88] Subsequently, another phase II clinical study of BV (open-label, multicenter, investigator-initiated) demonstrated significant and durable clinical activity. Among a total of 25 patients with r/r EBV-positive lymphomas (including 22 cases of mature T/NK-cell neoplasms), the ORR was 48%, with a median follow-up of 20 months. For the intention-to-treat population, OS and PFS were 15.7 months and 6.2 months, respectively.[41] In addition, two case reports have suggested that patients with refractory NKTCL achieved CR after BV therapy without significant toxicity.[89,90] Recently, according to another RCT that recruited 25 patients with r/r $CD30^+$ and EBV^+ lymphomas, the ORR for mature NKTCL was 46% and it was even higher in patients with mature B-cell lymphomas (67%). The duration of response was 10.1 months and the most common TRAEs were peripheral neuropathy and neutropenia.[41] Given its durable clinical activity and manageable toxicity, BV might have a promising future in treating r/r NKTCL as salvage therapy.

Table 1. Summary of available targets for natural killer/T cell lymphoma

Targets	Intervention/ treatment	Signal crosslinking	Structure	Prognostic relevance	Percentage of NKTCL with positive expression	Research stage for NKTCL	Reference
PD-1	Pembrolizumab	PD-1/PD-L1, LMP1, MAPK, JAK-STAT and NF-κB	Humanized IgG4	NA	NA	clinical	Li et al.[28]
	Nivolumab		Humanized IgG4			clinical	Chan et al.[29]
	Tislelizumab		Humanized IgG4			clinical	Tao et al.[30]
	Sintilimab		Humanized IgG4			clinical/preclinical	Yan et al., Wen et al.[31,32]
	Toripalimab		Humanized IgG4			clinical	
PD-L1	Avelumab	PD-1/PDL1, LMP1, MAPK, JAK-STAT and NF-κB	Humanized IgG1	Disputed	39%–100%	clinical	Nagato et al., Huang et al., Kim et al., Jo et al., Panjwani et al., Han et al.[33–38]
	Sugemalimab		Humanized IgG4			clinical	
	IMC-001		Humanized IgG1			clinical	
CTLA-4	Ipilimumab		Humanized IgG1	NA		clinical	Hosseini et al.[39]
CD25/IL-2Rα	Basiliximab	IL-2, LMP1, MAPK and NF-κB	Murine/human IgG1	Negative	NA	clinical	Wang et al.[40]
CD30	Brentuximab vedotin	NF-κB, MAPKs	Humanized IgG1	Disputed	50%–70%	clinical	Kim et al., Zhang et al.[41,42]
CD38 (TNFRSF8)	Daratumumab	calcium, BCR, TLR	Human IgGκ	Negative	95%	clinical	Lund, Wang et al., Huang et al., Hari et al., Huang et al.[43–47]
CD52	Alemtuzumab	IL-15	Humanized IgG1	NA		clinical	Kim et al., Zhang et al.[48,49]
CD56	huN901-DM1	NA		NA	~100%	preclinical	Ishitsuka et al.[50]
CCR4	Mogamulizumab	CCL17/CCR4, CCL22/CCR4	Humanized IgG1	NA	47%	preclinical	Kumai et al., Kanazawa et al.[51,52]
EBV antigens (LMP1/LMP2)	LMP-CTLs			NA		clinical	
CAR-T	anti-CD30 CAR-T			NA		clinical	
	anti-CD38 CAR-T			NA		preclinical	Li et al.[53]
	anti-CD7 CAR-T			NA		clinical	
	anti-CD19 CAR-T			NA		clinical	

NKTCL, natural killer/T cell lymphoma; PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IL-2Rα, IL-2 receptor alpha; EBV, Epstein-Barr virus; CTL, cytotoxic T lymphocyte; LMP1/2, Latent membrane protein 1/2; MAPK, Mitogen-activated protein kinases; JAK-STAT, Janus kinase-signal transducer and activator of transcription; NF-κB, Nuclear factor-κB; CCR4, C-C chemokine receptor 4; CAR-T, Chimeric antigen receptor T-cell; NA, data not available.

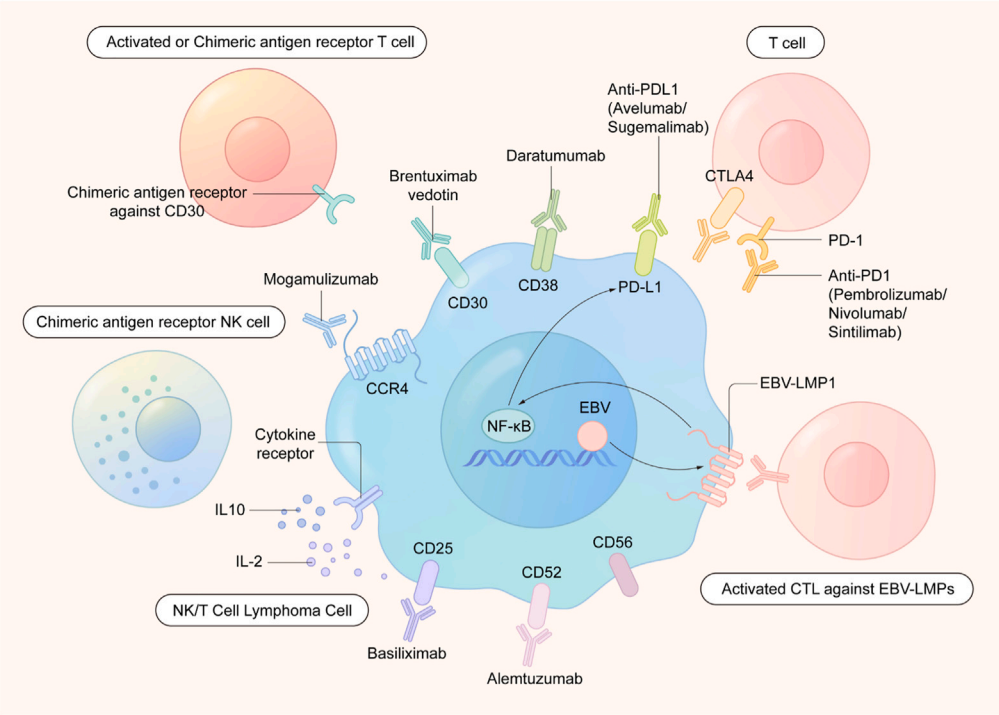

Figure 3. Summary of immunotherapy drugs or cells in NKTCL and their respective cellular membrane targets

Anti-PD1/PD-L1 antibodies, such as pembrolizumab, nivolumab, sintilimab, sugemalimab, and avelumab. Monoclonal antibodies target cellular membrane antigens or receptors, which include brentuximab vedotin, basiliximab, alemtuzumab, and daratumumab. Latent membrane protein 1 (LMP1) is a transmembrane protein produced by Epstein-Barr virus (EBV), which subsequently activates the NF-κB pathway and leads to cell proliferation and lymphomagenesis. This in turn upregulates PD-L1, which makes immune checkpoint blockade an attractive target. Engineered chimeric antigen T-cells (CAR-T) and EBV-CTLs are feasible for the treatment of NKTCL.

Anti-CD38 monoclonal antibody

CD38 is a type II transmembrane glycoprotein belonging to a complex family of enzymes on the cell surface and is related to the functions as a receptor and adhesion molecule.[43,91] Previous gene expression profile data revealed that CD38 gene expression was upregulated, and the antigen CD38 was highly expressed in approximately 50% of NKTCL, which is associated with poorer outcomes.[44,92] Due to its aberrant expression and involvement in regulating cellular metabolic pathways and immunomodulation, CD38 appears to be a promising target for treating NKTCL.[93] Several novel monoclonal antibodies with specific targeting of CD38 have been successfully developed, including daratumumab, isatuximab (SAR650984), and MOR202.[45,94] Hari and colleagues reported a case in which a patient with relapsed NKTCL achieved a sustained remission of 21 weeks as salvage therapy with single-agent daratumumab.[46] In a multicenter phase II trial, daratumumab was administered to 32 patients with r/r NKTCL. The ORR observed was 25.0%, and the median OS reached 141.0 days (NCT02927925). Furthermore, it has been reported that a high CD38: complement inhibitory protein (CIP) ratio in NKTCL might potentially predict a more favorable response to daratumumab.[95] In conclusion, while trials have provided initial insights, the available evidence remains limited, underscoring the need for further studies to inform the clinical application of anti-CD38 monoclonal antibodies.

Anti-CD52 monoclonal antibody

CD52 (CAMPATH-1 antigen) is a small glycoprotein expressed on lymphocytes, NK cells, dendritic cells (DCs), and macrophages. CD52 molecules provide costimulatory signals for lymphocyte activation and proliferation, as well as stimulate the production of IL-6, IFN, and TNF.[96,97] The expression of CD52 has been reported in up to 47% of patients with NKTCL, thus representing an attractive target for immunotherapy of EBV-induced lymphoma.[98] Alemtuzumab, a humanized IgG1 monoclonal antibody against CD52, was combined with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), producing 1 CR among 3 patients with newly diagnosed NKTCL.[99] Kim et al. reported that different doses of alemtuzumab combined with dexamethasone, cytarabine, and cisplatin (DHAP) for treating r/r PTCL (including 8 NKTCL subjects). ORR was observed in 24 patients (50%), with five CR and seven PR. The most common adverse event was grade 3/4 leukopenia (79.2%). Given its antitumor efficacy and tolerability, combining alemtuzumab plus DHAP might be an effective salvage treatment.[48] Findings from a phase II RCT (NCT00069238) suggested that alemtuzumab combined with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) resulted in stable remission in patients with CD52-positive NKTCL; 24 (77.4%) patients among 31 subjects achieved a response: 17 patients with CR and 7 subjects with PR. More recently, a phase III clinical trial (NCT00725231) was conducted to investigate the

Table 2. Clinical trials of immune monoclonal antibodies in natural killer/T cell lymphoma

Targets	Intervention/treatment	Disease	Trial name	Number of enrolled participants	Phase	Status	Trial identifier
PD-1	Pembrolizumab	T cell Lymphoma or NK-Cell Lymphoma	Pembrolizumab for T/NK-cell lymphomas NK-cell Lymphomas	33	2	Unkonwn	NCT03021057
		NKTCL of the nasal cavity/nasopharynx	Study of Pembrolizumab in Patients With Early-Stage NK/T cell Lymphoma, Nasal Type	19	2	Recruiting	NCT03728972
	Pembrolizumab	Relapsed/Refractory PCTL include NKTCL	Pembrolizumab and Pralatrexate in Treating Patients With Relapsed or Refractory Peripheral T cell Lymphomas	40	1/2	Recruiting	NCT03598998
	Pembrolizumab	Natural Killer/T cell Lymphoma, Nasal and Nasal-Type	Treatment of Relapsed or Refractory Natural Killer/T cell Lymphoma	20	2	Unkonwn	NCT03107962
	Pembrolizumab, Copanlisib	NK and T cell non-Hodgkin's lymphoma	Study of MK-3475 Alone or in Combination With Copanlisib in Relapsed or Refractory NK and T cell Non-Hodgkin Lymphoma	19	1/2	Active, not recruiting	NCT02535247
	Tislelizumab	NK/T cell Lymphoma	Dexamethasone, Azacytidine, Pegaspargase and Tislelizumab for NK/T cell Lymphoma	50	2	Not yet recruiting	NCT04899414
		Early-stage Extranodal NK-T-Cell Lymphoma, Nasal and Nasal-Type	Radiotherapy and Anti-PD-1 in Low-risk ES-ENKTCL	30	2	Recruiting	NCT05149170
	Sintilimab	Relapsed/Refractory ENKTL	Efficacy and Safety Evaluation of IBI308 in Patients With Extranodal NK/T cell Lymphoma Patients (ORIENT-4)	28	2	Completed	NCT03228836
	Sintilimab, P-Gemox	NK/T cell Lymphoma Nos	Sintilimab With P-GemOx Regimen for Newly Diagnosed Advanced Extranodal Natural Killer/T cell Lymphoma, Nasal Type	63	2	Recruiting	NCT04127227
	Sintilimab, Lenalidomide	NK/T cell Lymphoma Nos	Lenalidomide and Sintilimab for Relapsed/Refractory NK/T cell Lymphoma	20	2	Recruiting	NCT04231370
	Sintilimab, Chidamide	Relapsed/Refractory ENKTL	Sintilimab in Combination With Chidamide in Refractory and Relapsed ENKTCL	40	1/2	Completed	NCT03820596
	Sintilimab, Pegaspargase, Anlotinib	Early stage NKTL, nasal and nasal-Type	Combined Treatment of Sintilimab, Peg-aspargase Plus Anlotinib in NK/T cell Lymphoma	30	2	Recruiting	NCT03936452
	Pegaspargase, Anti-PD-1 monoclonal antibody	ENKTCL, nasal type	Anti-PD-1 Antibody Combined With Pegaspargase in the Treatment of Advanced Stage NK/T cell Lymphoma	22	2	Recruiting	NCT04096690
	PD-1 antibody, Chidamide, Lenalidomide, Etoposide	NK/T cell Lymphoma	PD-1 Antibody, Chidamide, Lenalidomide and Etoposide for Relapsed or Refractory NK/T cell Lymphoma	50	4	Unknown	NCT04038411
	Nivolumab	Relapsed/Refractory PTCL	Nivolumab in Treating Patients With Relapsed or Refractory Peripheral T cell Lymphoma	12	2	Terminated	NCT03075553

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Table 2. *Continued*

Targets	Intervention/treatment	Disease	Trial name	Number of enrolled participants	Phase	Status	Trial identifier
	Nivolumab	T cell and NK cell lymphomas, cutaneous squamous cell carcinoma, Merkel cell carcinoma, and other rare skin tumors	Talimogene Laherparepvec and Nivolumab in Treating Patients With Refractory Lymphomas or Advanced or Refractory Non-melanoma Skin Cancers	68	2	Recruiting	NCT02978625
	SHR-1210	Relapsed/Refractory ENKTCL, nasal type	SHR-1210 in Patients With Relapsed or Refractory Extranodal NK/T cell Lymphoma	97	2	Active, not recruiting	NCT03363555
	SHR1210, Apatinib	Relapsed/Refractory NKTCL	PD1 Combined With Apatinib in Patients With Relapsed or Refractory NK/T cell Lymphoma	61	2	Unknown	NCT03701022
	LEAP regimen (Sintilimab, Pegaspargase, Anlotinib)	Natural Killer/T cell Lymphoma, Nasal and Nasal-Type	Sintilimab, Pegaspargase and Anlotinib for Stage IV Natural Killer/T cell Lymphoma	37	2	Recruiting	NCT04004572
	Toripalimab	Extranodal NK/T cell Lymphoma, Nasal Type	Maintenance Therapy With Anti-PD-1 Antibody for Patients With NK/T cell Lymphoma	20	2	Not yet recruiting	NCT04338282
	Toripalimab, P-GemOx, IMRT	Early-Stage ENKTL	A Multicenter, Phase 3, Randomized Trial of Sequencial Chemoradiotherapy With or Without Toripalimab (PD-1 Antibody) in Newly Diagnosed Early-Stage Extranodal Natural Killer/T cell Lymphoma, Nasal Type (ENKTL)	207	3	Recruiting	NCT04365036
PD-L1	Avelumab	Relapsed/Refractory ENKTL	Avelumab in Relapsed or Refractory Extranodal Natural Killer/T cell Lymphoma[AVENT STUDY]	21	2	Active, not recruiting	NCT03439501
	Sugemalimab (CS1001)	Extranodal Natural Killer/T cell Lymphoma	A Study of CS1001 in Subjects With Relapsed or Refractory Extranodal Natural Killer/T cell Lymphoma (ENKTL)	80	2	Active, not recruiting	NCT03595657
	IMC-001	Relapsed/Refractory ENKTL	A Study of IMC-001 in Subjects With Relapsed or Refractory Extranodal NK/T cell Lymphoma, Nasal Type	20	2	Recruiting	NCT04414163
	Sugemalimab	Extranodal NK/T cell Lymphoma	An Expanded Access Program to Provide Sugemalimab for the Treatment of Relapsed or Refractory Extranodal Natural Killer/ T cell Lymphoma (R/R ENKTL)	NA	NA	Available	NCT05131438
CTL-4	Ipilimumab	Recurrent Melanoma, Non-Hodgkin Lymphoma, Colon, or Rectal Cancer, include Adult Nasal Type Extranodal NK/T cell Lymphoma	Ipilimumab and Local Radiation Therapy in Treating Patients With Recurrent Melanoma, Non-Hodgkin Lymphoma, Colon, or Rectal Cancer	3	1/2	Terminated (Planned Future Study)	NCT01769222
CCR4		Peripheral T/NK-cell Lymphoma		38	2	Completed	NCT01192984

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Table 2. *Continued*

Targets	Intervention/treatment	Disease	Trial name	Number of enrolled participants	Phase	Status	Trial identifier
	Mogamulizumab (KW-0761)		Study of KW-0761 in Subjects With CCR4-positive Peripheral T/NK-cell Lymphoma				
	KW-0761	Adult T cell Leukemia and Lymphoma (ATL), Adult Peripheral T cell Lymphoma (PTCL)	Phase I Study of KW-0761 in Relapsed Patients With CCR4-Positive ATL and PTCL	16	1	Completed	NCT00355472
CD25 (IL-2Rα)	Basiliximab	Mature T cell and NK-Cell Non-Hodgkin Lymphoma, Recurrent Mature T- and NK-Cell Non-Hodgkin Lymphoma, Refractory Mature T cell and NK-Cell Non-Hodgkin Lymphoma, Recurrent Cutaneous T cell Non-Hodgkin Lymphoma, Refractory Cutaneous T cell Non-Hodgkin Lymphoma	Yttrium Y 90 Basiliximab and Combination Chemotherapy Before Stem Cell Transplant in Treating Patients With Mature T cell Non-Hodgkin Lymphoma	20	1	Active, not recruiting	NCT02342782
	Basiliximab, Pegaspargase	Extranodal NK/T cell Lymphoma	Combination of Basiliximab and Pegaspargase in the Treatment of ENKTCL	20	2	Not yet recruiting	NCT04337593
CD30	B-MAD chemotherapy	Extranodal NK/T cell Lymphoma	B-MAD Chemotherapy in Newly-diagnosed Extranodal NK/ T cell Lymphoma	36	1/2	Active, not recruiting	NCT03246750
	Anti-CD30/CD16A Monoclonal Antibody AFM13	Recurrent or refractory CD30-positive HL or NHL	Modified Immune Cells (AFM13-NK) and A Monoclonal Antibody (AFM13) in Treating Patients With Recurrent or Refractory CD30 Positive Hodgkin or Non-Hodgkin Lymphomas	30	1	Recruiting	NCT04074746
	AFM 13	Relapsed/Refractory cutaneous lymphomas	AFM13 in Relapsed/Refractory Cutaneous Lymphomas	18	1/2	Completed	NCT03192202
	Brentuximab vedotin, Cyclophosphamide, Prednisone, Doxorubicin, Vincristine	Lymphoma, Large-Cell, AnaplasticLymphoma, NK-cellLymphoma, T cell	A Phase 1 Study of Brentuximab Vedotin Given Sequentially and Combined With Multi-Agent Chemotherapy for CD30-Positive Mature T cell and NK-Cell Neoplasms	39	1	Completed	NCT01309789
	Brentuximab vedotin	Relapsed or Refractory EBV-and CD30-positive Lymphomas	Brentuximab Vedotin in Patients With Relapsed or Refractory EBV-and CD30-positive Lymphomas	25	2	Completed	NCT02388490
CD38	Daratumumab	Relapsed or refractory NKTCL	A Study to Assess the Clinical Efficacy and Safety of Daratumumab in Participants With Relapsed or Refractory Natural Killer/T cell Lymphoma (NKTCL), Nasal Type	32	2	Completed	NCT02927925
CD52				31	2	Completed	NCT00069238

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Table 2. *Continued*

Targets	Intervention/treatment	Disease	Trial name	Number of enrolled participants	Phase	Status	Trial identifier
	Alemtuzumab (Campath), EPOCH	Lymphoma, T-CellLymphoma, Extranodal NK-T-Cell	Campath-1H and EPOCH to Treat Non-Hodgkin's T- and NK-Cell Lymphomas				
	Alemtuzumab, CHOP	T cell LymphomaLymphoma, Non-Hodgkin's	Study of CHOP + Campath for T cell, Null Cell, or Natural Killer (NK)-Cell Lymphoma	NA	1	Completed	NCT00161590
	Alemtuzumab, CHOP	Aggressive T/NK-Cell Lymphomas	CHOP and Campath-1H in Previously Untreated Aggressive T/NK-Cell Lymphomas	24	1	Completed	NCT00323323
	Alemtuzumab, CHOP-14	Peripheral T cell Lymphoma, Unspecified Angioimmunoblastic Lymphadenopathy Extranodal NK/T cell Lymphoma	Immunotherapy in Peripheral T cell Lymphoma - the Role of Alemtuzumab in Addition to Dose Dense CHOP (A-CHOP-14)	274	3	Unknown	NCT00725231

NKTCL, natural killer/T cell lymphoma; ENKTL, extranodal NK/T-cell lymphoma, nasal type; R/R, Relapsed/Refractory; PTCL NOS, peripheral T cell lymphoma not otherwise specified; HL, Hodgkin lymphomas; NHL, non-Hodgkin lymphomas; PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; CCR4, C-C chemokine receptor 4; IL-2Rα, IL-2 receptor alpha; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; P-GemOx, pegaspargase, gemcitabine and oxaliplatin; IMRT, intensity-modulated radiotherapy; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 3. Clinical trials of cellular treatment in natural killer/T cell lymphoma

Cellular treatment	Target	Intervention/ treatment	Disease	Trial name	Number of enrolled participants	Phase	Status	Trial identifier	Dose
CAR-T cells	CD7	CD7 CAR-T cells infusion	T-lymphoblastic Lymphoma, NK/T cell Lymphoma, Acute Lymphocytic Leukemia	CD7 CAR-T Cells for Patients With R/R $CD7^+$ NK/T cell Lymphoma, T-lymphoblastic Lymphoma, and Acute Lymphocytic Leukemia	10	Phase 1	Recruiting	NCT04004637	0.5-5×10^6/kg
		CD7-specific CAR gene-engineered T cells	T cell Acute Lymphoblastic Leukemia T cell Acute Lymphoblastic Lymphoma Acute Myeloid Leukemia NK Cell Lymphoma	Multi-CAR T cell Therapy Targeting CD7-positive Malignancies	30	Phase 1 and phase 2	Recruiting	NCT04033302	NA
		CD7 UCAR-T cells	$CD7^+$ T/NK Cell Hematologic Malignancies	Anti-CD7 U-CAR-T Cell Therapy for T/NK Cell Hematologic Malignancies	30	Early phase 1	Recruiting	NCT04264078	Three levels: 1×10^7 cells/kg, 3×10^7 cells/kg, 5 ×10^7 cells/kg
	CD30	Anti-CD30 CAR-T cells	Adult T cell Lymphoma/Leukemia, Anaplastic Large Cell Lymphoma, Angioimmunoblastic T cell Lymphoma, NK/T cell Lymphoma, Peripheral T cell LymphomaHodgkin Lymphoma	Anti-CD30 CAR-T Therapy in Patients With Refractory/Relapsed Lymphocyte Malignancies	50	Phase 1	Recruiting	NCT04008394	NA
		Anti-CD30 CAR-T cells, Cyclophosphamide, Fludarabine	Lymphoma, Large-Cell, Anaplasitc, Enteropathy-Associated T cell Lymphoma, Lymphoma, Large B-Cell, DiffuseLymphoma, Extranodal NK-T-Cell, Lymphoma, T cell, Peripheral	T Cells Expressing a Fully-Human Anti-CD30 Chimeric Antigen Receptor for Treating CD30-Expressing Lymphomas	26	Phase 1	Completed	NCT03049449	0.3x10^6 cells/kg (up to a maximum dose of 18x10^6 CAR+ T cells/kg)
		Anti-CD30 CAR T cells	Lymphomas	CAR T Cells Targeting CD30 Positive Lymphomas (4SCAR30273)	20	Phase 1 and phase 2	Unknown	NCT02274584	NA
		Anti-CD30 CAR-T cells	CD30 positive NHL subtypes (ALCL, PTCL-NOS, ENKTL, DLBCL-NOS, PMBCL)	Phase 1 Study of Autologous CD30.CAR-T in Relapsed or Refractory CD30 Positive Non-Hodgkin Lymphoma (CERTAIN)	21	Phase 1	Recruiting	NCT04526834	Three levels: 2 x 10^8 cell/m^2, 4 x 10^8 cell/m^2, 6 x 10^8 cell/m^2
		Anti CD30 CAR-T cells	Hodgkin Lymphoma, NK/T cell Lymphoma, Peripheral T cell Lymphoma, Unspecified; Angioimmunoblastic T cell Lymphoma, Anaplastic Large Cell Lymphoma, Diffuse Large B Cell Lymphoma, Mediastinal B-Cell Diffuse Large Cell Lymphoma, Gray Zone Lymphoma	An Exploratory Clinical Study Evaluating the Safety and Efficacy of Anti CD30 CAR T Cells in Patients With $CD30^+$ Relapsed/ Refractory Lymphoma	9	Early phase 1	Not yet recruiting	NCT05208853	Three levels: 1.5×10^7 cells, 1.5×10^8 cells, 5× 10^8 cells
		Activated/ stimulated T cells and LMP1/2-	Hodgkin Disease, Non Hodgkin Lymphoma, Lymphoepithelioma, Leiomyosarcoma	LMP-specific T-cells for Patients With Relapsed EBV-positive Lymphoma (ALCI)	74	Phase 1	Completed	NCT00671164	2 x 10^7 cells/m^2- 2 x 10^8 cells/m^2

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Table 3. *Continued*

Cellular treatment	Target	Intervention/ treatment	Disease	Trial name	Number of enrolled participants	Phase	Status	Trial identifier	Dose
		or LMP2-targeted strategies							
EBV-CTLs	LMP1/ LMP2 (EBV antigens)	Baltaleucel-T cells	EBV Positive Extranodal NK/T cell Lymphoma	Cellular Immunotherapy Treatment Antigen-Directed for EBV Lymphoma (CITADEL)	15	Phase 2	Terminated	NCT01948180	$2x10^7$ cells/m^2
		EBViNT Cells	EBV Associated Extranodal NK/T cell Lymphoma, EBV-Associated Gastric Carcinoma	A Multi-center, Single-arm, Open, Phase I/IIa Clinical Trial to Evaluate the Efficacy and Safety of EBViNT Cell (EBV Specific Autologous $CD8^+$ T cell) in Patients With Treatment Failed Epstein-Barr virus (EBV)-Positive Malignancies	72	Phase 1 and phase 2	Recruiting	NCT03789617	$1.4x10^9$ cells/ 100mL
		Epstein-Barr virus human cytotoxic T lymphocytes (EBV-CTLs)	Extranodal NK/T cell Lymphoma	VT-EBV-N for Treatment of Severe in EBV Positive Extranodal NK/T cell Lymphoma Patients	48	Phase 2	Recruiting	NCT03671850	NA

CAR-T, Chimeric antigen receptor T-cell; NHL, non-Hodgkin lymphomas; Anaplastic Large Cell Lymphoma; PTCL-NOS, peripheral T cell lymphoma not otherwise specified; ENKTL, Extranodal NK/T-cell Lymphoma; DLBCL-NOS, Diffuse Large B Cell Lymphoma not otherwise specified; PMBCL, Primary Mediastinal Large B-Cell Lymphoma; LMP1/2, Latent membrane protein 1/2.

Table 4. Selected reports of immunotherapy for natural killer/T cell lymphoma

Targets	Intervention/ treatment	Phase/ Study design	Disease	Sample size	Dosing	Treatment	ORR (%)	CRR (%)	Common AE	Median follow-up, mo (range)	Trial identifier	Reference
PD-1/PD-L1	Pembrolizumab	Retrospective	Relapsed or refractory after SMILE-like therapy	7	2 mg/kg every 3 weeks	Single agent	100%	71.40%	Grade 2 rush	6 (2–10)		Kwong et al.[59]
		Retrospective	Relapsed or refractory NKTCL	7	100 mg every 3 weeks	Single agent	57.10%	28.6%	All-grade AEs 71.4%	NA		Li et al.[28]
		Retrospective	Relapsed or refractory NHL (include 14 NKTCL)	30	100 mg or 200mg every 3 weeks	Single agent	NKTCL: 44%	–	Grade II skin rash, bowel perforation	NA		Kim et al.[121]
	Nivolumab	Retrospective	Relapsed or refractory after SMILE-like therapy	3	40 mg (the smallest vial available) every 2 weeks	Single agent, low dose	100.00%	66.70%	NA	NA		Chan et al.[29]
	Sintilimab	Phase 2	Relapsed or refractory ENKTL	28	200mg every 3 weeks	Single agent	75.0%	21.4%	Decreased lymphocyte count (46.5%), pyrexia (42.9%), and decreased white blood cell count (35.7%)	30.4 (27.5–31.9)	NCT03228836	Tao et al.[58]
	Avelumab	Phase 2	Relapsed or refractory ENKTL	21	10 mg/kg on days 1 and 15 of a 28-day cycle	Single agent	38.0%	24.0%	Fever (29%), anorexia (10%), Infusion-related reaction (19%)	15.7 (95% CI: 14.5–16.9)	NCT03439501	Kim et al.[61]
	Sugemalimab	Phase 2	Relapsed or refractory ENKTL	80	1200 mg	Single agent	45.6%	30.4%	–	18.7	NCT03595657	Huang et al.[34]
CCR4	Mogamulizumab (KW-0761)	Phase 2	CCR4-positive Peripheral T/NK-cell Lymphoma	37	1.0 mg/kg once weekly for 8 weeks	Single agent	35.0%	14.0%	Lymphocytopenia (81%), neutropenia (38%), leukocytopenia (43%), and pyrexia (30%)	NA	NCT01192984	Ogura et al.[122]
			Relapsed/ refractory peripheral T cell lymphoma	35	1.0 mg/kg once weekly for 4 weeks	Single agent	11.40%	3.00%	Drug eruption (34.2%), pyrexia (23.7%), diarrhea (18.4%), and pruritus (18.4%)	NA	–	Zinzani et al.[123]

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Table 4. *Continued*

Targets	Intervention/ treatment	Phase/ Study design	Disease	Sample size	Dosing	Treatment	ORR (%)	CRR (%)	Common AE	Median follow-up, mo (range)	Trial identifier	Reference
CD30	Brentuximab vedotin	Phase 1	Refractory or relapsed HL or CD30$^+$ NHL	24	SGN-30 at 4 dose levels (2, 4, 8, or 12 mg/kg) weekly for 6 consecutive weeks	Single agent	Modest efficacy	4.16%	Nausea (13.0%), fatigue (13.0%), and fever (13.0%)	NA	NCT00051597	Bartlett et al.[124]
		Phase 1	Relapsed or refractory CD30-positive hematologic cancers	45	0.1 to 3.6 mg/kg every 3 weeks	Single agent	67.0%	24.4%	Fatigue (36%), pyrexia (33%), and diarrhea, nausea, neutropenia, and peripheral neuropathy (22% each)	NA	NCT00430846	Younes et al.[125]
		Phase 2	Relapsed/ refractory CD30$^+$ NHL	34	1.8 mg/kg every 3 weeks	Single agent	41.0%	23.5%	Neutropenia (14%), peripheral sensory neuropathy, and hyperkalemia (9% each)	2.7 (0.3–17.3)	NCT01421667	Horwitz et al.[126]
		Cases	ENKTL with CD30 expression	2	1.8 mg/kg every 3 weeks	Single-agent	–	–	Grade 2 toxicity dyspnea	–	–	Kim et al., Poon et al.[89,90]
		Phase 2	Relapsed or Refractory EBV- and CD30-positive Lymphomas	25	1.8 mg/kg every 3 weeks	Single-agent	48.0%	20.0%	Peripheral neuropathy (48%), neutropenia (44%), thrombocytopenia (20%), and rash (16%)	20 (1.7–30.4)	NCT02388490	Kim et al.[41]
CD38	Daratumumab	Phase 2	Relapsed or refractory ENKTL	32	16 mg/kg once weekly for Cycles 1 and 2, every other week for Cycles 3 through 6, and every 4 weeks thereafter, all cycles were 28 days	Single agent	25.0%	–	Thrombocytopenia (25.0%), neutropenia (18.8%), and anemia and leukopenia (15.6%)	10.2 months	NCT02927925	Huang et al.[45]
		Case	A patient with stage IV NKTCL	1	16 mg/kg weekly	Single agent	Patients reached a maximum sustained remission period of 21 weeks.	–	Multiple infectious complications (were considered unrelated to daratumumab)	NA	–	Hari et al.[46]

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Table 4. *Continued*

Targets	Intervention/ treatment	Phase/ Study design	Disease	Sample size	Dosing	Treatment	ORR (%)	CRR (%)	Common AE	Median follow-up, mo (range)	Trial identifier	Reference
CD52	Alemtuzumab	Phase 2	Newly diagnosed PTCL (inlude 3 ENKTL)	3	10 mg i.v. on day 1 and 20 mg i.v. on day 2 in the Wrst cycle, then 30 mg i.v. on day 1 in the subsequent cycles	Combined with CHOP	80.0%	65.0%	Neutropenia (90%), febrile neutropenia (55.0%), cytomegalovirus reactivation (25%)	7 (1–12)	–	Kim et al.[99]
		Phase 2	Relapsed or refractory PTCL after first-line therapy	8	70 mg or 40 mg	Combined with DHAP	50.0%	29.1%	Leukopenia (79.2%)	NA	–	Kim et al.[48]
EBV antigens (LMP1/ LMP2)	Activated/ stimulated T cells	Phase 1	EBV-associated lymphoma	50	2 x 10^7-3 x 10^8 cells/m^2	LMP-Specific CTLs As Adjuvant Therapy	–	–	There were no clinical toxicities associated with the CTLs	NA	NCT00671164	Bollard et al.[107]
IMiDs	Thalidomide	Prospective, single center	T-NHL (include 21 NKTCL)	46	200 mg (range, 150–400 mg) every night	Combined with chemotherapy	79.2%	50.0%	Without reported severe side effects	NA	–	Wu et al.,[127]

PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1; C-C chemokine receptor 4; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide; DHAP, dexamethasone, cytarabine, and cisplatin; HL, Hodgkin lymphomas; NHL, non-Hodgkin lymphomas; NKTCL, natural killer/T cell lymphoma; ENKTL, extranodal NK/T-cell lymphoma; AEs, adverse events; CCR4, C-C chemokine receptor 4; PTCL, peripheral T cell lymphoma; IMiDs, immunomodulatory drugs; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ORR, objective response rate; CRR, complete response rate; OS, overall survival; NE, not estimable; 95% CI, 95% confidence interval; NA, data not available.

value of adjuvant alemtuzumab in combination with dose-dense CHOP-14 in patients with previously untreated PTCL (including NKTCL), which might provide new evidence on alemtuzumab treatment.

The anti-CD52 mAb seems to be an attractive candidate for treatment optimization; however, significant treatment-related adverse events cannot be overlooked. More recent studies have focused on improving the safety profile of alemtuzumab and its efficacy in combination with other therapies. Trials involving the application of alemtuzumab in patients with NKTCL are currently being conducted (NCT00161590, NCT00323323, and NCT00118352).

Anti-CCR4 monoclonal antibody

C-C chemokine receptor 4 (CCR4) is expressed on Th2 cells, Tregs, or EBV-infected NK cells of EBV-related hematologic malignancies and belongs to the G-protein-coupled receptor family.[100,101] CCR4 is commonly expressed in various NKTCL cell lines, such as SNK6, SNK10, SNK1, NKL, and HANK1.[51,102,103] Elevated expression of the CCR4 ligands, CCL17 (TARC) and CCL22 (MDC), expression was reported in patients with NKTCL. Therefore, the CCL17/CCL22-CCR4 axis seems to be an attractive immune therapeutic target for aggressive NKTCL.[51]

Mogamulizumab, a monoclonal antibody of CCR4, targets CCR4-expressing malignant cells by ADCC and depletes Tregs in the tumor microenvironment.[104] Kanazawa et al. confirmed that mogamulizumab induced ADCC against CCR4-expressing cells and prevented EBV-positive NK-cell lymphomas from growing in murine models.[52] The trial findings of 26 aggressive adult patients with T cell leukemia-lymphoma suggested the potential antitumor activity and notable OS and PFS of mogamulizumab (NCT00920790).[105] In 2018, mogamulizumab was approved by the FDA for treating mycosis fungoides or Sézary syndrome in patients who were treated with at least one prior systemic therapy. While anti-CCR4 monoclonal antibodies have primarily been studied in T cell NHL, further research is warranted to provide more evidence on antitumor efficacy and tolerability in NKTCL.

ADOPTIVE T/NATURAL KILLER-CELL THERAPY

Epstein-Barr virus-related antigen-specific cytotoxic T lymphocytes

Antigen-specific cytotoxic T lymphocyte therapy can induce durable antitumor activity in specific tumors, such as lymphomas and melanoma.[106,107] Previous reports have shown that over 90% of the patients with NKTCL have a latent infection of EBV in tumor cells.[108,109] High expression of EBV proteins, LMP1/LMP2 and Epstein-Barr virus nuclear antigen 1 provides appealing targets for adoptive immunotherapy with EBV-CTLs in NKTCL.[110,111] Data from one trial of patients with EBV-positive lymphomas (enrolled 11 patients with NKTCL) undergoing autologous EBV-specific T cell therapy reported sustained clinical responses at a median of 3.1 years in 13 of 21 patients with lymphoma, including CRs in 4 of 6 patients with r/r NKTCL.[107] Another clinical trial reported that adoptive transfer of EBV LMP1/2a-specific CTLs for NKTCL is an effective post remission therapeutic approach without immediate or delayed toxicities. Ten of 11 subjects who received LMP1/2a CTLs achieved sustained CR after induction chemotherapy, with 100% 4-year OS and 90% PFS (median follow-up, 55.5 months).[112] Another phase II trial revealed that patients with aggressive NKTCL who failed asparaginase-based regimens utilizing autologous EBV-specific T cells (47 subjects enrolled, of whom 15 patients were successfully generated and infused with baltaleucel T) achieved an ORR of 50.0% and a CR rate of 30.0%, with a median PFS of the patients was 12.3 months. Diarrhea, vomiting, pyrexia, and headache were the most frequent AEs.[113]

Although preclinical/clinical results demonstrated that adoptive EBV-CTL transfer is a promising treatment strategy in NKTCL, the clinical utility may be limited by the long turnaround time and high manufacturing failure rate. An off-the-shelf bank of donor-derived EBV-CTLs is being developed, and if the risk of graft versus host can be minimized, it might be an attractive and unprecedented option.[114–116] Table 3 summarizes the clinical trials of cellular immunotherapy for NKTCL.

Chimeric antigen receptor cell-based immunotherapy

Chimeric antigen receptor T cell therapy

Chimeric antigen receptor T (CAR-T) cell therapy has been proven to be a successful immunotherapy that has achieved remarkable efficacy in some relapses or refractory hematologic malignancies.[117] Tang et al. demonstrated that targeting LMP1 utilizing HELA/CAR cells might be a promising cellular therapy for treating EBV-positive malignancies.[118] CD38-CAR-T cells exhibited substantial inhibition against diverse lymphocyte malignancies, including NKTCL, mantle cell lymphoma, and T cell acute lymphoblastic leukemia, in both *in vitro* and mouse xenograft models.[119] In a recent preclinical study, four CAR-T cell lines (CD38-CAR, LMP1-CAR, CD38-LMP1 tandem CAR 1 and CD38-LMP1 tandem CAR 2) exhibited significant cytotoxicity against NKTCL cells both *in vitro* and *in vivo*.[53] Another preclinical investigation suggested that NKTCL cell lines expressed high levels of B7-H3 homogeneously. Anti-B7-H3/CD3 bispecific T cell engaging and B7-H3-redirected CAR-T cells have demonstrated potent *in vitro* antitumor efficacy and induced tumor regression in NKTCL tumor mouse models.[120] Currently, an ongoing phase I trial (NCT03049449) is designed to provide data on the safety and feasibility of utilizing fully human anti-CD30 CAR cells for the treatment of patients with advanced CD30-expressing lymphomas. While the data from clinical trials for CAR-T therapy in NKTCL are currently limited and in their nascent stages, the outlook is promising. Several research are underway to investigate the efficacy of the combination of anti-CD7/CD30 CAR-T cells and other treatments for NKTCL (NCT04004637, NCT04008394, NCT03049449, NCT02274584, NCT03910842, and NCT04033302).

Although CAR-T therapy is a powerful strategy for treating hematological malignancies, there are still many patients who do not respond to the therapy. Of note, life-threatening CAR-T cells therapy toxicities, especially cytokine release syndrome (CRS) and neurologic toxicity, should be addressed. To overcome the limitations of CAR-T cell therapy, researchers must identify the most suitable patients, improve clinical efficacy, and decrease the related toxicity, and innovative strategies and approaches are thus critical.

Immune system modulators

Immunomodulatory drugs (IMiDs) demonstrate potential benefits via anti-inflammatory properties, immunomodulatory effects, and anti-proliferative effects. IMiDs (e.g., thalidomide and lenalidomide) exhibited antitumor activity in multiple lymphomas and demonstrated a potential therapeutic activity in NKTCL (Table 4). Previous studies have shown that the immunomodulatory activity of lenalidomide depends on increasing levels of IL-2 and antiangiogenic. Wang et al. revealed that one NKTCL patient previously treated with an asparaginase-containing regimen in combination with radiotherapy exhibited no response to autologous stem cell transplantation, but it was a successful salvage therapy in which the patient was treated with lenalidomide monotherapy and obtained a CR.[128] Additionally, the combination of thalidomide with the CHOP regimen has demonstrated increased efficacy and the potential to decrease the occurrence of adverse gastrointestinal side effects.[127] Du et al. reported three patients with r/r NKTCL treated with the combination regimen of toripalimab, chidamide, etoposide, and thalidomide. Two patients achieved CR and another patient obtained PR, with controllable TRAEs, such as grade 2/3 leukocytopenia and anemia.[129] The combination of thalidomide with dexamethasone-containing therapy has also been shown to have potential therapeutic benefits. The V140A variant of the evolutionarily conserved signaling intermediate in the Toll pathway (ECSIT) activated the NF-κB pathway, leading to hyperinflammation, and promoted hemophagocytic syndrome (HPS) in NKTCL. Thalidomide prevented the NF-κB pathway from binding to the DNA promoters of the target genes, revealing the feasibility of combination with dexamethasone-containing therapy in two patients with NKTCL with HPS.[130] To date, data from studies regarding the efficacy of IMiDs are still limited. In a phase III RCT (NCT02085655), the efficacy and safety of P-Gemox in combination with thalidomide was compared with AspaMetDex (pegaspargase, methotrexate, and dexamethasone) in previously untreated or patients with r/r NKTCL. Other trials to further explore the use of IMiDs in NKTCL are ongoing (NCT04231370, NCT05058755, NCT04038411, and NCT03054532). Collectively, findings from the IMiDs provide mechanistic insights and a potential therapeutic strategy for NKTCL.

CONCLUSION

Although the outcomes of early-stage diseases have been remarkably improved due to asparaginase-based regimens, there remains an urgent need for novel and additional therapies in relapsed/refractory NKTCL. Immunotherapy, including monoclonal antibodies and adoptive T cell therapy, has rapidly transformed the treatment landscape, offering unprecedented therapeutic efficacy. Challenges persist, including selecting patients who could respond well to the treatment and identifying molecular markers to predict further prognoses, still need to be solved. Results of the underway preclinical and clinical research may help to better understand the safety and efficacy of immunotherapy. Collectively, with deeper insight into immunotherapy for NKTCL, it is hoped that future studies will further optimize immunotherapies for patients with NKTCL to achieve better therapeutic responses and minimize side effects.

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AUTHOR CONTRIBUTIONS

LH and NC wrote the review, XCP and LD provided critical suggestions, LH refined the final draft of the review.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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