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CURRENT OPINION

EBV-associated NK and T-cell lymphoid neoplasms

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Purpose of review
Epstein-Barr virus (EBV)-associated neoplasms derived from natural killer (NK) or T cells comprise a group of clinically and biologically heterogenous disorders affecting children and adults, which are overall rare but more prevalent in Asia and South America. This review focuses on neoplasms presenting in the adulthood, addressing recent genomic discoveries as well as therapeutic developments in these highly aggressive disorders.

Recent findings
Distinct molecular subtypes of extranodal NK/T-cell lymphomas (ENKTCLs) have been described, with differences in cell of origin, EBV pattern, genomic alterations, clinical characteristics, response to asparaginase-based therapies and to more recent approaches targeting molecular aberrations of the lymphoma. For the last two decades, progress in the clinical management of ENKTCL was based on L-asapraginase containing combinations and the incoroperation of radiotherapy. A subset of cases with *PDL1-2* structural alterations may be more responsive to treatment with immune checkpoint inhibitors. Primary nodal EBV+ lymphomas derived from T or NK cells have distinctive features separating them from both peripheral T-cell lymphoma not otherwise specified and ENKTCL. Treatment algorithms correspond to those for advanced ENKTCL.

Summary
With better understanding of lymphomagenesis, genomic landscape and immunologic aspects of the diseases, future treatment options will include targeted therapies including immune checkpoint inhibitors and novel antibodies.

Keywords
Epstein-Barr virus, NK/T-cell lymphoma, pathogenesis, pathology, treatment

INTRODUCTION

Epstein-Barr virus (EBV)-positive lymphoproliferative disorders of NK or T cells are overall uncommon diseases, which are more prevalent in Asia and central and South America. Several entities are currently recognized, all characterized by distinctive clinical presentations affecting preferentially children or adults, selective lineage derivation, and variable natural histories and outcome (Table 1, Fig. 1) [1,2]. In this review, we will focus on the three entities manifesting in the adulthood, and summarize the recent advances in the understanding of EBV-associated lymphomagenesis, progress in the deciphering of molecular pathogenesis, therapeutic innovations and current clinical recommendations.

MECHANISMS OF EPSTEIN-BARR VIRUS-ASSOCIATED NK AND T-CELL LYMPHOMAGENESIS

EBV is an oncovirus that belongs to the gammaherpes subfamily. EBV is transmitted through saliva, and occasionally causes infectious mononucleosis in adolescents and young adults. Nearly, 90% of adults become infected with EBV, so EBV is a ubiquitous virus. However, in a limited number of cases, EBV causes a variety of malignancies, including lymphomatoid and epithelial tumors.

EBV was originally isolated from Burkitt lymphoma in 1964 [3]. Since that discovery, the

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Curr Opin Oncol 2022, 34:422–431

DOI:10.1097/CCO.0000000000000889

KEY POINTS

- Viral oncogenes, such as LMP1 and LMP2A, promote the proliferation or inhibit the apoptosis of EBV-infected NK and T cells
- Genomic instability caused by EBV infection induces somatic mutations in oncogenes and tumor suppressor genes, promoting the development of EBV-associated NK and T-cell lymphomas.
- Extranodal NK/T-cell lymphoma may be divided into three molecular subtypes defined on the basis of cell of origin, EBV gene expression, transcriptional signature, and responses to asparaginase-based regimens and targeted therapy ; and into four tumor immune microenvironment subgroups which may serve as a useful biomarker for immunotherapy
- Primary nodal EBV-associated lymphoma derived from T or NK cells has distinctive features which warrant the consideration of a distinctive disease entity

pathogenesis of Burkitt lymphoma has been extensively studied. EBV infects germinal center B cells via CD21. The viral glycoprotein gp350/220 binds to the complement receptor, CD21, whereas gH/gL/gp42 binds to HLA class II molecules, both of which are expressed on the surface of B cells [4]. Viral oncogenes, such as latent membrane proteins (LMPs) and EBV-encoded nuclear antigens, promote the proliferation or inhibit the apoptosis of infected cells. Then, genetic mutations accumulate with the help of activation-induced cytidine deaminase (AIDs) or co-factors [3]. Finally, *MYC* is translocated and activated, and Burkitt lymphoma develops. Other than Burkitt lymphoma, EBV is associated with several types of B-cell malignancies, such as Hodgkin lymphoma, lymphomatoid granulomatosis, EBV-positive diffuse large B-cell lymphoma, not otherwise specified (DLBCL), and posttransplant lymphoproliferative disorders [4].

In contrast, the pathogenesis of EBV-associated NK and T-cell lymphoma is not fully understood. For example, how EBV infects NK and T cells has not been clarified, given that NK and T cells do not express the CD21 receptor molecule. EBV infects epithelial cells using integrins and Ephrin-A2 as receptors [5]. Although these proteins are abundant on epithelial surfaces, their roles in EBV infection of lymphoid cells, including NK and T cells, are limited. Okuno *et al.* reported that the same somatic driver mutations are recognized in EBV-infected T and NK cells in some patients with chronic active EBV infection who carry both EBV+ T and NK cells [6▪]. The results indicate that different cell lineages share identical driver mutations, suggesting a common ancestry. EBV may infect common lymphoid progenitor cells that express CD21. These cells differentiate into NK and T cells in some patients with chronic active EBV infection. It is also reported that intragenic EBV deletions are frequently detected in chronic active EBV infection, extranodal NK/T cell lymphoma (ENKTCL), and EBV-positive DLBCL patients [6▪]. Peng reported that similar deletions are frequently seen in ENKTCL patients in China [7]. Thus, intragenic EBV deletions are common in certain types of EBV-associated lymphomas and could be associated with lymphomagenesis [8,9].

There are several possible reasons why EBV-associated NK and T-cell lymphoma is more prevalent in East Asia and Central and South America. First, environmental factors, such as chemical solvents and exposure to pesticides, are potential carcinogens in patients with ENKTCL [3]. Second, genetic factors, such as human leukocyte antigen (HLA) alleles, may contribute to lymphomagenesis. For example, HLA-A1, which is common in Caucasian but not Chinese populations, is a risk factor for the development of EBV-positive Hodgkin lymphoma. In contrast, HLA-A02 : 07 is associated with nasopharyngeal carcinoma, which is common in East Asia. Third, EBV strains that are prevalent in specific areas may differentially increase the risk of certain tumor types. Although many EBV variants (including single nucleotide polymorphisms) have been reported to enhance tumorigenicity, there are no definitive causative genes [10]. All of these factors may interact in a complex manner to trigger the development of EBV-positive tumors.

After EBV infects NK and T cells, the infected cells proliferate with the help of viral oncoproteins. LMP1, which mimics CD40, constitutively activates the AKT, STAT, JNK, MAPK, and NF-κ B pathways and thereby suppresses apoptosis, enhances cell cycling, and modulates the immune system [3]. LMP2A, which mimics the B-cell receptor, triggers sustained activation of AKT, Syk, β-catenin, and protein kinase C, and thus promotes cell proliferation and suppresses differentiation [3]. Both LMP1 and LMP2A are expressed in EBV-infected NK and T cells. Other EBV genes have pivotal roles in lymphomagenesis. BHRF1 is a homolog of BCL-2 that promotes cell proliferation [11]. Interestingly, particular EBV genes, such as *BNRF1*, *BGLF5*, and *BALF3*, increase genomic instability in cells; BALF3 has terminase activities [12▪▪,13,14]. Furthermore, an EBV infection can activate AIDs. LMP1 triggers genomic instability through increased expression of AIDs, which promotes somatic hypermutations and class switch recombination [3]. Such genomic instability caused by EBV infection induces somatic

Table 1. Synoptic summary of EBV-associated lymphoproliferative disorders derived from NK or T cells [2]

Entity	Age group	Cell derivation	Characteristics	Outcome
Systemic EBV-positive T-cell lymphoma of childhood	Children East Asia and Latin America, rare in Europe	T cells	Fatal infectious mononucleosis / fulminant hematophagocytic syndrome, marked lymphoid EBV+ infiltration in several affected organs	Rapid fatal, fulminant course with hemato lymphoid histiocytosis and multiorgan failure
Chronic active EBV disease (T and NK-cell phenotype)	Children East Asia, less commonly Latin America	T cells or NK cells	Disease with mononucleosis-like symptoms during more than 3 months, fever, hematophagocytic syndrome, hepatitis, high titers of EBV in blood, organ infiltration by EBV+ small cells	Indolent lymphoproliferative disorders, worse for T-cells derived cases. However, some cases may evolve to ENKTCL or ANKCL
Hydroa vacciniforme lymphoproliferative disorder	Children and adolescents Classic form: more common in whites Systemic form: more common in Asians and Latin Americans	T cells more often than NK cells	Classic form: photoreactive cutaneous vesicular disorders Systemic form: general symptoms, fever, lymphadenopathy, frequent liver involvement	Classic form: self-limited Systemic type: may progress to T or NK lymphoma or develop hemophagocytic syndrome
Severe mosquito bite allergy	Children East Asia and Mexico	NK cells	Cutaneous form of chronic active EBV infection: exaggerated allergic reaction to mosquito bites	May progress to ENKTCL or ANKCL.
Extranodal NK/T-cell lymphoma, nasal type (ENKTCL)	Adults More common in East Asia, Central & South America. Less common in Europe	NK cells more than T cells	Angiocentric and angiodestructive lymphoma, cytotoxic, with necrosis; variable cytomorphology; usual presentation in the nasal area or other extranodal sites	Aggressive disease, variable outcome, worse for nonnasal cases
Primary EBV-positive nodal T-cell or NK-cell lymphoma	Adults and elderly, immunosuppression and HIV Very rare	T cells more than NK cells	Nodal involvement, usually disseminated, associated immunodeficiency in some patients, monomorphic or pleomorphic	Poor outcome, worse than ENKTCL
Aggressive NK-cell leukemia (ANKCL)[a]	Adults Asia, central and South America Very rare	NK cells	Acute presentation with fever, systemic symptoms, hepatosplenomegaly, intravascular disseminated coagulation or hematophagocytic syndrome; systemic proliferation of EBV+ NK cells in blood bone marrow and other organs	Usually fulminant, or subacute in a subset of cases

[a]some cases EBV-negative. ANKCL: aggressive NK-cell leukemia; ENKTCL: extranodal NK/T-cell lymphoma.

mutations in oncogenes and tumor suppressor genes, resulting in the development of EBV-associated NK and T-cell lymphomas.

PATHOLOGY, MOLECULAR/GENETIC FEATURES, AND SUBGROUPS

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL) is an EBV-positive lymphoma derived from NK cells more often than cytotoxic T cells [15] with a high prevalence in Asian and Latin American populations. Genome-wide association studies have identified three susceptibility loci (*HLA-DPB1*, *HLA-DRB1* and *IL18RAP*) associated with increased risk of developing ENKTCL [16,17▪].

The genomic landscape of ENKTCL is complex. In addition to numerous copy number variations, notably very frequent del (6)(q21-q25) including candidate tumor suppressor genes [18], large scale sequencing studies of several Asian cohorts and one Latin American cohort have highlighted frequent activating mutations of the JAK-STAT pathway (most frequently *STAT3,* less commonly *JAK3* or *STAT5B)*, recurrent mutations in epigenetic modifiers (*KMT2C*, *KMT2D*, *TET2*), and recurrent mutations in *DDX3X* (an RNA helicase gene), *BCOR*

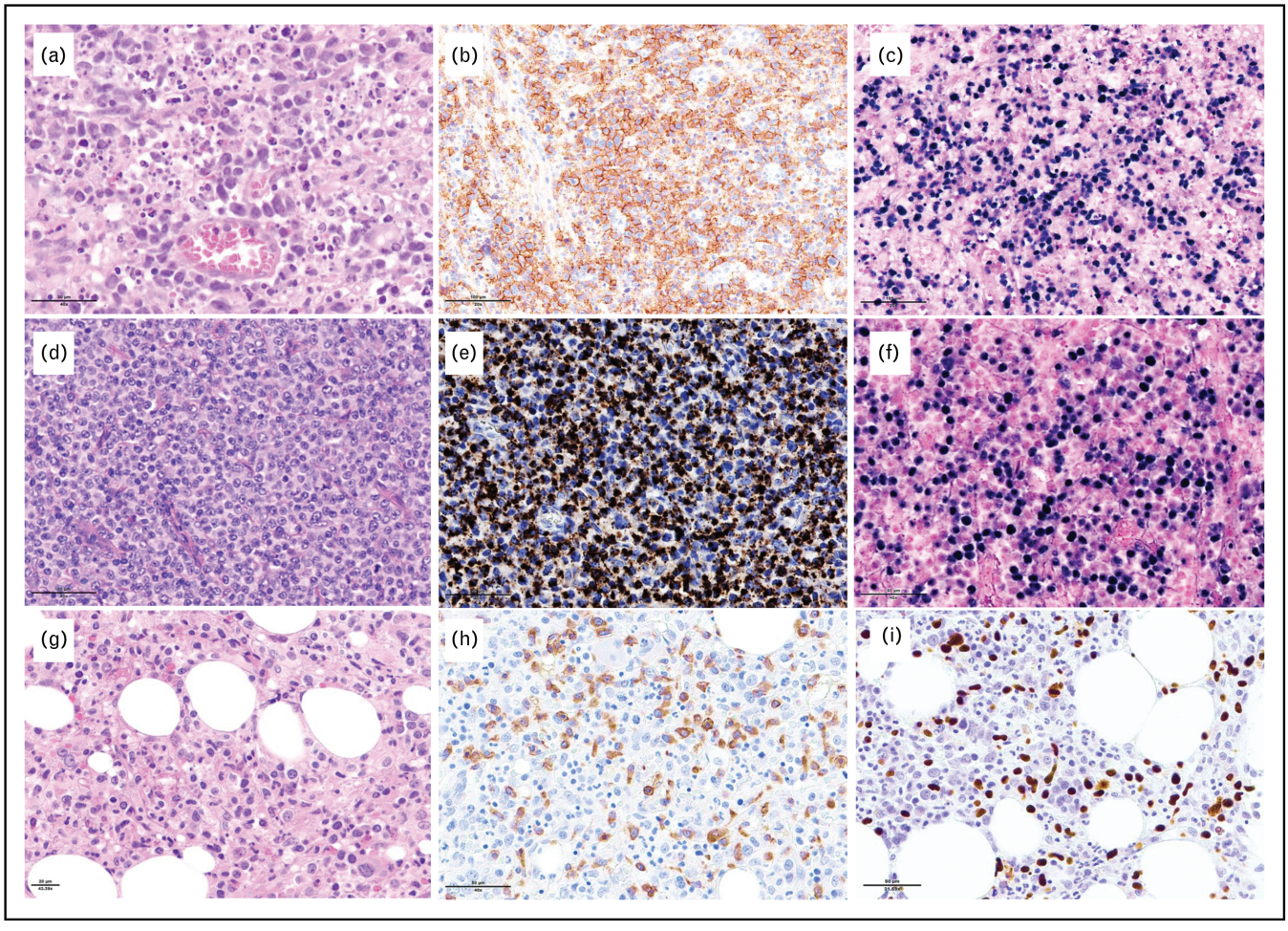

FIGURE 1. Histology of extranodal NK T-cell lymphoma (a-c), primary nodal EBV+ T/NK-cell lymphoma (d-f) and aggressive NK-cell leukemia (g-i). (a-c): ENKTCL involving the intestine, showing a pleomorphic large cell neoplasm (a), positive for CD56 (b) and EBV (in situ hybridization)(c); (d-f): primary nodal EBV+ T/NK-cell lymphoma: diffuse proliferation of large cells featuring an immunoblastic to centroblastic morphology (d); strong expression of granzyme B is seen throughout the tumor (e); in-situ hybridization with EBER probes shows positivity in most nuclei (f); (g-i): bone marrow involvement in a case of aggressive NK-cell leukemia: H&E stain shows hypercellular bone marrow and scattered hypochromalic cells with irregular and sometimes elongated nuclei (g); the atypical cells are well highlighted by an immunostain against CD3 (h) and are positive for EBER by in-situ hybridization (i). Original magnifications, x200 to x400.

(encoding a co-repressor of *BCL6)*, and *TP53* [19,20]. The relative prevalence of these mutations varies according to studies, with a higher frequency of *STAT3* mutations in Latin American cases, and differences reported according to the NK versus T-cell lineage [12▪▪,20]. Mutations in *DDX3X TP53* and *KMT2D* have been reported to correlate with a worse prognosis [12▪▪,21].

One study has addressed the utility of circulating cell-free DNA (cfDNA) genotyping in high-risk ENKTCL patients and found that at baseline plasma cfDNA had a sensitivity of 72% in detecting mutations also found in tumor biopsies, and allowed the detection of additional mutations; moreover longitudinal analyses under treatment of high-risk patients suggests that plasma cfDNA could represent a noninvasive approach to monitor treatment response and predict survival [22].

A large multiomics study of ENKTCL biopsies defined three prominent molecular subtypes. The TSIM subtype mostly derived from NK cells, had mainly alterations in tumor suppressor (*TP53* and del6q21) and immune modulators (*JAK/STAT* mutations/amplifications (17q21.2) and *PDL1-2* amplifications (9p24.1) The MYC-related (MB) subtype was enriched in *MGA* mutations and LOH at the *BRDT* locus, associated with MYC expression and tumor dissemination, had the worst outcome. The histone epigenetic altered (HEA) subtype characterized by aberrant histone acetylation, correlated with T-cell

lineage, was enriched in mutations in *EP300, ARID1A, HDAC9*, and had the best outcome [12▪▪].

Frequent PD-L1 expression is reported in ENKTCL tumors, with different studies having produced heterogeneous results regarding the frequency of PD-L1 positivity and its prognostic significance (favorable, unfavorable or with no effect on overall survival) [23]. Blood cell analyses seem to be more consistent in findings of higher concentrations of serum soluble PD-L1 (sPDL-1) being associated with adverse clinicopathological factors and poor treatment response or outcome [24,25]. Structural variants disrupting the 3′ UTR region of *PD-L1* and focal gains or amplifications of the gene locus have been described in 20–23% of the cases [26], result in high PD-L1 expression by immunohistochemistry and were found to predict sensitivity to immune checkpoint inhibitors (ICI) [27] which has emerged as a promising therapeutic strategy in ENKTCL patients [28,29]. Specifically, in one study where whole genome sequencing was performed on 19 tumors from relapsed/refractory ENLTCL patients who were treated by pembrolizumab, the four tumors harboring *PD-L1* structural variants (21%) were from patients who responded to the treatment (4/9), while none of the nonresponders (0/10) had a *PD-L1* alteration [27].

In a recent study, Cho *et al.* analyzed the tumor immune microenvironment of ENKTCL by mRNA profiling and immunohistochemistry. They identified distinct subgroups: (i) immune-tolerance, characterized by high Treg counts, frequent early stage disease and nasal localization; (ii) immune evasion (A and B) showing high cytotoxic T-cell counts, high PD-L1 expression and low T-reg counts; and (iii) immune silenced, characterized by immune exhaustion, linked to advanced stage disease and poor prognosis. Interestingly, analysis of the small subset of patients who were treated with pembrolizumab in that study, indicates that immune silenced tumors were non responders (0/%) while 4/6 patients from the other subgroups responded to therapy, suggesting that these microenvironment subgroups may represent biomarkers of response for immunotherapy [30▪].

Primary EBV+ nodal T/NK cell lymphoma classified as a variant of peripheral T-cell lymphoma (PTCL), NOS in the 2017 WHO classification [31], is segregated as a provisional separate entity in the 2022 International Consensus Classification [2]. This rare disease involves lymph nodes while lacking nasal involvement and tends to occur in elderly adults, in association with HIV infection or immunodeficient conditions [32–34]. Pathological features distinct from ENKTCL include a monomorphic large cell morphology, less frequent necrosis, negativity for CD56, positivity for CD8, and more frequent derivation from T cells than from NK cells [34,35]. Few cases have been investigated by high-throughput sequencing; recurrent mutations have been found in *TET2*, *DNMT3A*, *STAT3*, *PIK3CD* and *DDX3X* [35,36▪▪]. A recent publication focused on the genomic findings in 77 cases, found that primary EBV+ nodal T/NK cell lymphoma is characterized by poor outcome, low genomic instability, upregulation of immune pathways (checkpoint protein PD-L1) that promote immune evasion, and downregulation of EBV miRNAs [36▪▪].

Aggressive NK-cell leukemia (ANKCL) is a very rare and usally highly aggressive disseminated malignancy derived from NK cells, most often (but not always) associated with EBV infection. While earlier studies disclosed a pattern of chromosomal imbalances distinct from that of ENKTCL, recent NGS studies have shown overlapping characteristics in the mutational landscape of ANKCL and ENKTCL. The most frequently mutated genes include *TET2* (25–30%), *CREBBP* (15–20%) *TP53* (30–35%), *STAT3* (20%) or other genes of the JAK/STAT pathway [37,38▪,39,40]. One study suggested that lack of *TP53* mutation might identify patients following a subacute rather than fulminant clinical course [37].

STANDARD THERAPY AND NEW DEVELOPMENTS

For patients with early-stage disease

More than 70% patients with ENKTCL are early-stage at their first diagnosis, with radiotherapy playing a crucial role in successful therapy of such patients [41]. However, a considerable proportion of patients treated with radiotherapy alone are refractory or eventually relapse [41]. Combined modality therapy (CMT) including chemotherapy and radiotherapy improves outcome and is recommended for stage I/II disease [42,43].

Li *et al.* established a prognostic model consisting of age, performance status, stage, primary tumor invasion, lactate dehydrogenase, and found radiotherapy alone is a proper strategy for patients of the low-risk group [41,44]. More recently, a prognostic index of natural killer lymphoma (PINK) based on age, stage, nonnasal-type disease, distant lymph node involvement, and PINK with detectable Epstein-Barr virus DNA in blood (PINK-E) were developed to improve risk-adapted therapy [45]. Impressively, a comprehensive molecular nomogram model comprised of seven-single nucleotide polymorphism-based classifier and clinicopathological prognostic factors was constructed to help individualized treatment based on the risk scores for

localized ENKTCL and complement the current prognostic systems [46].

With the introduction of nonanthracycline-based therapeutic strategies, the prognosis of patients with ENKTCL has significantly improved [47▪▪]. However, the optimal CMT strategy remains controversial due to the lack of large-scale, randomized controlled trials (RCT) comparing the three frequently used CMT protocols [sequential chemoradiotherapy, concurrent chemoradiotherapy (CCRT), and sandwich chemoradiotherapy.

Common CCRT protocols, such as radiotherapy, concurrently with DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) [48] or ESHAP (etoposide, steroid, high-dose Ara-C, and platinum) followed by ESHAP alone [49] or pegaspargase [50], CCRT followed by VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) [51] or VIDL (etoposide, ifosfamide, dexamethasone, and L-asparaginase) [52] demonstrated therapeutic efficacy. Unfortunately, many patients develop long-term adverse events associated with CCRT, especially on oral and nasal mucosa, which can substantially reduce patients' quality of life [53] (Table 2). Sandwich chemoradiotherapy was similarly effective in early-stage ENKTCL compared to sequential chemoradiotherapy, but with higher incidence of grade 3 or 4 hematological AEs [54]. Chemotherapy regimens included in sandwich chemoradiotherapy are LVP (L-asparaginase, vincristine, and prednisone) [55] and MESA (methotrexate, etoposide, dexamethasone, and pegaspargase) [56].

Sequential chemotherapy combined with radiotherapy showed similar clinical outcome compared with CCRT [57]. A large retrospective multicenter study analyzing sequential P-GEMOX (pegaspargase, gemcitabine and oxaliplatin) and radiotherapy for localized ENTKL, reported a complete response rate and objective response rate (ORR) of 83% and 96% with 3-year progression-free survival and overall survival of 75% and 85%, respectively, which was similar with historical cohorts; however, the incidences of severe hematological toxicities and radiation-induced mucositis were lower than reported for CCRT. Furthermore, a sequential modified SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) and radiotherapy [58], radiotherapy followed by GDP [59], P-GEMOX/GELOX (L-asparaginase plus gemcitabine and oxaliplatin) followed by radiotherapy [60], sequential DICEL (dexamethasone, ifosfamide, cisplatin, etoposide, and L-asparaginase) and radiotherapy [61], sequential DDGP (pegaspargase, gemcitabine, cisplatin and dexamethasone) and radiotherapy [62] were alternative therapeutic protocols. Efficacy and adverse events related to the regimens were listed in Table 2.

In summary, radiotherapy in combination with chemotherapy is essential for successful treatment of newly diagnosed localized ENKTCL. Risk-adapted treatments based on prognostic models contribute to optimize individual therapy.

For patients with advanced and relapsed or refractory (r/r) disease

Chemotherapy is generally regarded as the optimal salvage treatment for advanced and r/r ENKTCL. The main chemotherapy regimens include SMILE [63,64], P-GEMOX [65,66], and AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) [67] with subsequent radiotherapy of residual lesions being an option. The SMILE regimen has shown remarkable clinical efficacy in advanced and r/r ENKTCL, but the hematological toxicity is relatively significant, and the nonhematological toxicity, such as renal function damage, can be significant [63,64,68]. Experienced physicians surveying all supportive treatment are needed to minimize the potential side-effects of this regimen. The P-GEMOX regimen demonstrated considerable efficacy comparable to that of the AspaMetDex regimen, with less toxicity and thus seems more convenient for clinical application [65].

High PD-L1 expression on tumor cells is an independent risk factor for poor prognosis in patients with ENKTCL [69,70]. Anti-PD-1 antibodies exhibit unique efficacy in r/r ENKTCL, and results of several small sample size studies show that pembrolizumab and nivolumab can result in satisfactory ORRs of 57%∼100% [28,29,71–73]. In a phase 2 clinical trial, sintilimab monotherapy demonstrated an ORR of 68%, and a 2-year OS rate of 79% in r/r ENKTCL [72]. The efficacy of PD-1 antibody combined with P-GEMOX regimen in advanced ENKTCL is promising, with an ORR of 89%, and the side effects are all manageable [74]. The SCENT study reported that the ORR of sintilimab combined with the histone deacetylase inhibitor (HDACi) chidamide was 58% in r/r ENKTCL, and the complete response rate reached 44%, indicating that it can be used as a new therapeutic option for r/r patients [75].

Avelumab, an anti-PD ligand 1 (PD-L1) antibody, had a CR rate of 24%, and an ORR of 38% in r/r ENKTCL [76]. Another PD-L1 antibody, CS1001, also showed promising efficacy in r/r ENKTCL with an ORR of 43% [77], suggesting that further exploration of the therapeutic value of PD-L1 antibody combination therapy is required.

Several retrospective studies have also indicated that autologous or allogeneic hematopoietic stem

Table 2. Efficacy and grade 3 or more adverse events associated with treatment

Treatment	stage	CR/ORR	PFS	leukopenia	neutropenia	FN	anemia	thrombocytopenia	anorexia	mucositis	stomatitis	nausea or vomiting	liver injury	infection	renal injury
RT-DeVIC[48]	I/II	82%/89%	5y 61%	NR	NR	17%	NR	NR	2%	NR	38%	1%	NR	5%	NR
CCRT+ESHAP[49]	I/II	92%/100%	2y 90%	NR	92%	69%	77%	69%	NR	46%	NR	8%	0%	8%	8%
CCRT-pegaspargase[50]	I/II	100%/ 100%	2y 93%	13%	NR	NR	3%	0%	0%	0%	NR	0%	0%	NR	NR
CCRT +VIPD[51]	I/II	80%/83%	3y 85%	0%+47%	NR	0%+ 60%	0%+ 27%	0%+23%	0%+0%	NR	0%+0%	3%+7%	NR	0%+7%	NR
CCRT+VIDL[52]	I/II	87%/NR	5y 73%	0%+86%	NR	0%+ 18%	0%+ 11%	0%+14%	0%+0%	NR	17%+ 21%	0%+11%	0%+11%	NR	NR
LVP+RT+LVP[55]	I/II	81%/88%	2y 81%	8%	NR	NR	0%	0%	NR	23%	NR	0%	0%	NR	NR
P-GEMOX/GELOX+RT [60]	I/II	NR/93%	5y 56%	NR	25%	NR	13%	19%	NR	NR	NR	6%	0%	NR	NR
P-GEMOX+RT[87]	I/II	83%/96%	3y 75%	NR	25%	NR	4%	15%	NR	13%	NR	3%	5%	NR	NR
RT+GDP[59]	I/II	89%/95%	3y 77%	37%	34%	NR	5%	12%	NR	25%	NR	2%	0%	0%	0%
DICEL+RT[61]	I/II	91%/100%	5y 89%	76%	NR	27%	9%	3%	12%	6%	NR	12%	0%	NR	NR
DDGP+RT[62]	I/II	73%/83%	5y 83%	20%	NR	NR	20%	27%	NR	NR	NR	17%	3%	NR	0%
SMILE[63]	IV, r/r	45%/79%	1y 53%	100%	100%	NR	50%	64%	24%	13%	NR	18%	32% (AST elevation); 32% (ALT elevation);11% (hyperbilirubinemia)	61%[a]	5%
SMILE[64]	I/II/IV, r/ r	66%/81%	4y DFS64%	NR	67%	NR	NR	42%	NR	NR	NR	NR	7%	NR	1%
P-GEMOX[66]	All, r/r	59%/85%	median 61 mo	NR	28%	NR	7%	29%	NR	NR	NR	0%	7%	NR	NR
AspaMetDex[67]	r/r	61%/78%	median 12.2mo	NR	42%	11%	21%	5%	NR	NR	NR	NR	16%	11%	0%

ALT, alanine transaminase; AST, aspartate transaminase; CR, complete response; DFS, disease-free survival; FN, febrile neutropenia; mo, months; NR, not reported; ORR, objective response rate; PFS, progression-free survival; r/r, relapsed or refractory; y, year(s).
[a]two patients died.

Table 3. Targeted agents in clinical trials and case reports for the treatment of ENKTCL

Target	Targeted agent	No. of patients	ORR	CR	Reference
PD-1	Pembrolizumab	7	100%	29%	[28]
PD-1	Pembrolizumab	7	57%	29%	[29]
PD-1	Sintilimab	34	75%	21%	[72]
PD-1	Sintilimab+ P-GEMOX	9	89%	78%	[74]
PD-1	Sintilimab+ chidamide	36	58%	44%	[75]
PD-L1	Avelumab	21	38%	24%	[76]
PD-L1	CS1001	32	43%	33%	[77]
CD38	Daratumumab	32	25%	0%	[82]
CD30	Brentuximab vedotin	7	29%	14%	[84]
CD30	Brentuximab vedotin	1	NR	CR	[83]
CD25	Basiliximab	1	NR	PR	[88]
HDACi	Chidamide	19	50%	31%	[89]
Proteasome inhibitor	Bortezomib+ GIFOX[a]	7	43%	14%	[90]
Exportin 1 (XPO1)	Selinexor	7	57%	29%	[75]
EBV-CTLs	–	11	50%[b]	13%	[86]
JAK/STAT inhibitor	Tofacitinib and chidamide	Data not yet published	Data not yet published	Data not yet published	NCT03598959
Pi3k inhibitor	–	–	Preclinical	Preclinical	–

[a]Three of the seven patients were early-stage ENKTCL.
[b]In six patients with predefined evaluable disease.

cell transplantation (HSCT) after high-dose chemotherapy could prolong the survival of ENKTCL patients [78–80].} However, the exact value of autologous HSCT remains controversial due to the small sample size and lack of convincing randomized controlled trial data.

With a better understanding of the molecular genetics and immune pathogenesis of ENKTCL, promising immunotherapies, and targeted therapies such as anti-CD38 antibody [81,82], anti-CD30 antibody [83,84], and antigen-specific EBV-cytotoxic T lymphocyte (CTLs) therapy have attracted great attention [85,86] (Table 3), potentially changing the landscape of treatment for ENKTCL. Although some of these approaches have yielded satisfactory results, more evidence from larger populations is required to validate its survival benefit and elucidate long-term toxicity before clinical application.

CONCLUSION

For the last 2 decades, the progress in the clinical management of ENKTCL patients was based on L-asapraginase-containing combinations and the incorporation of radiation therapy into treatment algorithms. With increasing knowledge on lymphomagenesis, including genomic landscape, and immunologic aspects of the disease, future developements will comprise more targeted approaches, including immune checkpoint inhibitors and novel antibodies.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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