Extranodal NK/T cell lymphoma

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Abstract

Extranodal natural killer (NK)/T cell lymphoma (ENKTL) is a distinct subtype of Non-Hodgkin's lymphoma mainly involving the nasal area. Since the entity was first recognized, treatment strategies have been evolving from anthracycline-based chemotherapy and radiotherapy to L-asparaginase containing regimens and recently immune checkpoint inhibitors. With the currently used combined chemotherapy and radiotherapy, more than 70% of patients with localized disease can be cured. L-asparaginase containing regimens have significantly improved treatment outcomes among patients with advanced disease. However, the treatment outcomes of patients with disease refractory to L-asparaginase containing regimens or who experience recurrence remain poor. In this article, we cover the current treatments for ENKTL and emerging treatment approaches.

Key Words Extranodal natural killer/T cell lymphoma, ENKTL, Non-Hodgkin's lymphoma, Immunotherapy

INTRODUCTION

Extranodal natural killer (NK)/T cell lymphoma (ENKTL), nasal type is a subtype of non-Hodgkin's lymphoma characterized by an association with Epstein–Barr virus (EBV) infection and extranodal involvement [1, 2]. The lymphoma cells originate from either NK cells or γδ T cells [3]. T cell receptor gene rearrangement is observed in 10–35% of patients [4]. Therefore, in the latest World Health Organization classification, these lymphomas are referred to as ENKTLs, to reflect their putative cellular origins from NK cells and T cells [5]. The invariable association of ENKTL with EBV and its pathogenic role were recognized in earlier studies [6-8]. EBV exists in a clonal episomal form and is not integrated into the host genome in ENKTL [9]. The distribution of normal NK cells along barrier surfaces explains the extranodal property of ENKTL. The incidence of ENKTL varies significantly among regions, being the highest in East Asia and Latin America where early childhood EBV infection is prevalent [10-12]. Clinically, ENKTL shows unique features and predominantly involves the nasal area as a progressive necrotic lesion; thus, it was previously referred to as "lethal midline granuloma". Pathologically, ENKTL had been referred to as polymorphic reticulosis or angiocentric lymphoma, because angiocentric and angio-invasive infiltrates are commonly present [13]. In this article, we summarize the current diagnosis and treatment of ENKTL and emerging treatment options.

CLINICAL FEATURES

ENKTL usually manifests as progressive ulceration and necrotic granuloma in the nasal cavity, palate, and nasopharynx, frequently causing palatal perforation [6, 7]. The tumor frequently invades around tissues such as facial skin, paranasal sinus, and orbits, and results in extensive destruction of midline lesions [1]. At presentation, the disease is often localized in the nose, nasopharynx, oropharynx, Waldeyer's ring, and upper aerodigestive tract; however, advanced disease may involve the skin, lymph node, liver, spleen, bone marrow, and peripheral blood [1]. The most common symptoms at the time of diagnosis are nasal obstruction and bloody rhinorrhea [8]. Swelling of the cheek or orbit, sore throat, and hoarseness are also major symptoms of ENKTL [8, 14]. In addition, systemic symptoms such as prolonged fever and weight loss are common [8]. ENKTL usually affects individuals aged about 40–50 years without gender predilection [1, 8].

DIAGNOSTIC WORKUP

Endoscopic examination and biopsy are crucial for the diagnosis of ENKTL [15]. Typically, the tumor lesion has extensive angioinvasion and necrosis, which often makes an accurate diagnosis difficult. Therefore, multiple biopsy samples are needed for better diagnosis. The tumor lesion is composed of a polymorphic population of atypical lymphoid cells, inflammatory cells, and eosinophils [10]. ENKTL cells express CD2, cytoplasmic CD3 (but not surface CD3), and CD45, as well as the NK cell marker CD56. Perforin, Fas ligand, and intercellular adhesion molecule-1 (ICAM-1) are also expressed in the tumor cells [13]. To diagnose ENKTL, the presence of EBV-encoded RNA by in situ hybridization should be confirmed along with either CD56 or cytotoxic molecules (granzyme B, perforin, or TIA1). In the absence of both, the diagnosis becomes EBV-positive peripheral T cell lymphoma, not otherwise specified [5].

A measurement of plasma EBV DNA titer by polymerase chain reaction is recommended at diagnosis. EBV DNA fragments are released into the blood when ENKTL cells undergo apoptosis [16]. This characteristic makes a measurement of plasma EBV DNA useful in determining tumor burden [17], real-time monitoring of treatment response [18], and prediction of recurrence during follow-up [19].

ENKTL is typically a fluorodeoxyglucose-avid lymphoma, and an analysis demonstrated that positron emission tomography/computed tomography (PET/CT) is superior to conventional staging methods (physical examination, CT with intravenous contrast, biopsies from primary sites, and bone marrow examinations) in detecting malignant lesions [20]. Therefore, PET/CT is currently regarded as the standard imaging modality for ENKTL. In addition, end of treatment PET/CT is useful for prognostication [19]. Thus, it should be performed for newly diagnosed patients as a baseline study.

PROGNOSTIC MODELS

Unlike other NHLs, the international prognostic index (IPI) does not discriminate among risk groups clearly in ENKTL. Most patients (81%) are classified into the low or intermediate risk group based on the IPI, because ENKTL has very unique clinical features presenting localized disease (76%), with rare involvement of bone marrow (6%), and high occurrence of constitutional symptoms even in localized disease (29%) [21]. Thus, a different prognostic model composed of four clinical prognostic factors (B symptoms, stage III/IV, elevated LDH, and regional LN involvement) was proposed for ENKTL (NK prognostic index) [1, 21]. This model had balanced distribution in each group (group 1, 27%; group 2, 31%; group 3, 20%; group 4, 22%) and predicted treatment outcomes better than did IPI. However, this prognostic model was based on the outcomes with anthracycline-containing regimens, so it is outdated. Since EBV

DNA titer has been recognized as a clinical progression/recurrence marker [22], another prognostic model based on post-treatment Deauville score on PET-CT scan and the presence of EBV DNA was evaluated [19]. In that study, both Deauville score 3 or 4 [progression-free survival (PFS) hazard ratio (HR), 3.607; 95% confidence interval (CI), 1.772–7.341; univariable $P < 0.0001$] and EBV DNA positivity (PFS HR, 3.595; 95% CI, 1.598–8.089; univariable $P < 0.0001$) were significantly associated with PFS and overall survival (OS). By combining the two prognostic factors, the model predicted PFS even better (for low risk vs. high risk, HR, 7.761; 95% CI, 2.592–23.233; $P < 0.0001$; for low risk vs. failure, HR, 18.546; 95% CI, 5.997–57.353; $P < 0.0001$). The most recently proposed prognostic index of NK lymphoma (PINK/PINK-E) was built from the clinical data of Asian patients, which uses EBV DNA titer as well as clinical parameters (age >60 yr, advanced stage, non-nasal type disease, and distant lymph node involvement) for risk stratification [23]. With the above mentioned models, a risk-adapted approach according to the risk groups should be evaluated with further studies.

TREATMENT OF LOCALIZED DISEASE

Standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by involved field radiotherapy (RT) showed disappointing outcomes as front-line treatment for ENKTL [24]. This is mainly attributed to the high expression of the multidrug resistance (MDR) related P-glycoprotein on ENKTL cells, which makes chemotherapeutic agents (doxorubicin and cyclophosphamide) ineffective [25, 26]. In addition, other MDR related proteins such as MDR-associated protein (MRP), and lung resistance-related protein are also expressed in ENKTL cells [27]. Poor drug penetration due to extensive tissue necrosis also hampers the effect of chemotherapy [28]. Therefore, non-anthracycline based combinations including agents such as methotrexate, ifosfamide, etoposide, gemcitabine, platinum, and L-asparaginase are used as front-line therapy.

L-asparaginase induced rapid apoptosis of neoplastic NK cells ex vivo due to their inability to synthesize asparagine [29]. L-asparaginase as a single agent was found to be effective for relapsed/refractory ENKTL [30]. Based on this finding, L-asparaginase combinations were tested as front-line treatment [31, 32]. A meta-analysis showed that the use of L-asparaginase was associated with better overall response rate (ORR) and complete remission (CR) rates in both localized and systemic ENKL [33].

RT showed better treatment outcomes as front-line therapy than CHOP [28], and the importance of radiation dosage was also shown in many studies [34-36]. Radiation dose less than 50 Gy produced inferior outcomes. However, RT alone is also not enough due to the high risk of systemic relapse [37]. Thus, combined chemotherapy and radiotherapy (concurrent or sequential) is currently considered as the standard treatment for patients with limited disease.

Concurrent chemoradiotherapy

In a phase I/II study, simultaneous application of RT (50 Gy) and a combination of the MDR non-related agents DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) was evaluated among 33 patients [38]. Of the 26 patients assessable for a response, the ORR and CR rate were 81% and 77%, respectively. In an updated analysis at a median follow-up of 67 months, the 5-year OS and PFS rates were 70% and 63%, respectively, with acceptable late toxicities [39].

In another phase II trial conducted by the Consortium for Improving Survival of Lymphoma, concurrent RT (40 Gy) and cisplatin (30 mg/m^2 weekly) followed by three cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) was evaluated among 30 patients [40]. The ORR was 83.3% and the CR rate was 80%. The 3-year OS and PFS rates were 86% and 85%, respectively. The addition of L-asparaginase to this strategy was tested in the following study [41]. Thirty patients were treated with concurrent radiotherapy (40 Gy) and cisplatin (30 mg/m^2 weekly) followed by 2 cycles of VIDL (etoposide, ifosfamide, dexamethasone, and L-asparaginase). The CR rate and ORR were 87% and 90%, respectively. With a median follow-up of 44 months, the estimated 5-year PFS rate was 73% and the rate of grade III/IV neutropenia was higher in the study than in the VIPD study (46.7% vs. 80%). The addition of L-asparaginase in the combination chemotherapy failed to improve treatment outcomes. In the next prospective study of the same group, 28 patients were assessed to evaluate concomitant use of L-asparaginase with concurrent chemoradiotherapy followed by two cycles of the MIDDLE (methotrexate, ifosfamide, dexamethasone, L-asparaginase, and etoposide) regimen. The overall treatment outcomes

were no better with higher grade III/IV neutropenia (91.3%) [42]. Another concurrent chemoradiotherapy comprising intensity modulated radiotherapy (56 Gy) with weekly cisplatin and 3 cycles of GDP (gemcitabine, dexamethasone, and cisplatin) consolidation was evaluated among 32 patients with localized nasal ENKTL [43]. The CR and 3-year OS rates were 84.4% and 84%, respectively, with a grade III/IV leukopenia rate of 41%.

A group of Japanese researchers recently reported promising results with intra-arterial infusion of chemotherapy with RT [44]. Three cycles of the MPVIC-P (methotrexate, peplomycin, etoposide, ifosfamide, carboplatin, and prednisolone) regimen were infused via the superficial temporal artery in combination with RT (54 Gy) among 12 patients with localized ENKTL. All the 12 patients achieved CR with manageable toxicities. With a median follow-up of 81 months, no relapse was observed among the patients. However, since the sample size was quite small, this strategy should be validated with further studies.

Sequential chemoradiotherapy

The efficacy of the SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) regimen was initially evaluated for patients with stage IV, relapsed or refractory ENKTL [45]. Based on the outstanding outcomes (ORR 79% and CR rate 45%) in advanced disease, the SMILE regimen is used for localized ENKTL as a part of chemotherapy and RT. The Asia Lymphoma Study Group assessed the real-world treatment outcomes of the SMILE regimen. In the analysis, the ORR and CR rate were 90% and 69%, respectively, at the end of the treatment among 29 patients with localized nasal ENKTL who received SMILE followed by RT [46]. Among them, 19 patients received SMILE with

Table 1. Treatment strategies for localized (stage IE/IIE) ENKTL.

Regimen	Treatment	N	ORR/CR (%)	OS/PFS (%)	Grade III/IV neutropenia (%)
Concurrent therapy					
DeVIC [38, 39]	Simultaneous RT 50 Gy+DeVIC×3	33	77/76	70/63 (5-yr)	91
VIPD [40]	CCRT (weekly cisplatin+RT 40–50.8 Gy)→VIPD×3	30	83/80	86/85 (3-yr)	47
VIDL [41]	CCRT (weekly cisplatin+RT 40–44Gy)→VIDL×3	30	90/87	60/73 (5-yr)	80
MIDDLE [42]	CCRT (weekly cisplatin, L-asparaginase×3+RT 36–44 Gy)→MIDDLE×2	28	86/82	82/74 (3-yr)	91
GDP [43]	CCRT (weekly cisplatin+IMRT 56 Gy)→GDP×3	32	91/84	88/84 (3-yr)	41 (leukopenia)
MPVIC-P [44]	Simultaneous RT 56 Gy+intra-arterial MPVIC-P	12	100/100	100/100 (5-yr)	33
Sequential therapy					
SMILE [44]	SMILE→RT→SMLIE	17	NA/82	NA	NA
LVP [32, 47]	LVP→IFRT→LVP	26	89/81	65/64 (5-yr)	31 (grade 3)
GELOX [31, 48]	GELOX→IFRT	27	96/74	86/86 (2-yr)	NA
P-GEMOX [49]	P-GEMOX×2→RT 56 Gy	33	94/80	83/77 (2-yr)	33.3
DICE-L [50]	DICE-L×3→RT 45 Gy	27	NA/91	89/82 (5-yr)	4.4 (leukopenia)

Abbreviations: CR, complete remission; ENKTL, Extranodal NK/T cell lymphoma; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial remission; RT, radiotherapy.

sandwiched RT. Grade III/IV neutropenia occurred in 57% of the patients despite the granulocyte colony stimulating factor (G-CSF) prophylaxis per protocol. Although chemotherapy followed by RT is convenient for the prompt application of therapy, the SMILE regimen should be used cautiously due to its higher rate of hematological toxicities.

Several other L-asparaginase-containing regimens were tested as sandwich treatment. LVP (L-asparaginase, vincristine, and prednisolone) [32, 47], GELOX (gemcitabine, L-asparaginase, and oxaloplatin) [31, 48], P-GEMOX (pegaspargase, gemcitabine, and oxaliplatin) [49], DICE-L-asp (dexamethasone, ifosfamide, cisplatin, etoposide, and L-asparaginase) [50], and MESA (methotrexate, etoposide, dexamethasone, and pegaspargase) [51] followed by RT showed similar outcomes in terms of response and survival (the CR rate and ORR ranged 74–91% and 92–100%, respectively, and the 5-year OS and PFS rates ranged 64–89% and 64–83%, respectively) [52].

Retrospective analyses of sequential treatment and concurrent treatment reported comparable outcomes [53, 54]. Therefore, both sequential chemotherapy and RT or concurrent chemoradiotherapy could be used as front-line treatment for localized ENKTL according to the clinical situation (Table 1).

TREATMENT OF ADVANCED STAGE AND REFRACTORY/RELAPSED DISEASE

L-asparaginase containing regimens are currently most widely used in the treatment of advanced ENKTL. In the initial study of SMILE, 20 patients with advanced ENKTL were included [45]. After 2 cycles of SMILE, the ORR and CR rate were 80 and 40%, respectively. With a median follow-up of 24 months, the 1-year OS and PFS rates were both 45%. All the patients developed grade III/IV neutropenia and there was a treatment-related mortality rate of 10%. This result was reproduced outside clinical trials. In a retrospective analysis including 26 patients with newly diagnosed stage IV ENKTL, SMILE induced CR in 53.8% of the patients. Grade III/IV neutropenia occurred in 65.5% of patients and there were 5 sepsis-related deaths. The 5-year OS rate was 47% and the 4-year disease-free survival rate was 60% [46]. In the application of SMILE to patients with ENKTL, the risk of hematological toxicities was a major concern. A retrospective analysis reported that GDP (gemcitabine, dexamethasone, and cisplatin) induced an ORR of 83% after a median of 6 cycles among patients with disseminated ENKL without causing grade III/IV febrile neutropenia [55]. In terms of treatment-related toxicities, the GDP regimen showed an advantage over the previous regimens.

Another L-asparaginase-containing regimen was evaluated in a phase II study that included 19 patients with relapsed/refractory ENKL [56]. After three cycles of AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) chemotherapy, the CR rate and ORR were 61%

and 78%, respectively. With a median follow-up of 26 months, the estimated 2-year OS and PFS rates were both around 40%. Only one patient experienced grade IV neutropenia.

Pegylated asparaginase containing regimens have been explored in ENKTL. In a retrospective study, MEDA (methotrexate, etoposide, dexamethasone, and pegaspargase) was evaluated among 13 patients with advanced stage and relapsed/refractory disease [57]. The reported CR rate and ORR were 62% and 77%, respectively, after 6 cycles. With a median follow-up of 20 months, the 1-year OS and PFS rates were 69% and 62%, respectively. Another study evaluated P-GEMOX (pegaspargase, gemcitabine, and oxaliplatin) among 21 patients with relapsed/refractory disease (9 patients with advanced stage) [58]. In the study, the CR rate and ORR were 52% and 81%, respectively. With a median follow-up of 17 months, the 3-year OS and PFS rates were 58% and 24%, respectively. In a randomized trial, DDGP (dexamethasone, gemcitabine, cisplatin, and pegaspargase) was compared with SMILE among patients with newly diagnosed advanced stage ENKTL [59]. Twenty-one patients in each group received 6 cycles of DDGP or SMILE. The 1-year PFS and 2-year OS rates were better in the DDGP group than in the SMILE group (86% vs. 38% for 1-year PFS, P=0.006; 74% vs. 45% for 2-year OS, P=0.027). The CR rate and ORR were higher in the DDGP group than in the SMILE group (71% vs. 29%, P=0.005 for CR rate; 95% vs. 67%, P=0.018 for ORR) with less hematological toxicities.

STEM CELL TRANSPLANTATION

The role of hematopoietic stem cell transplantation (HSCT) in the treatment of ENKTL has been explored in many studies. However, as most of these studies were small phase I, II, or retrospective analyses including very heterogeneous clinical settings with diverse protocols, interpreting the results is complicated.

The clinical outcomes of upfront auto-HSCT were analyzed in a retrospective study conducted in Korea [60]. The study included 62 patients with ENKTL (31 patients with advanced disease), and reported that at a median follow-up of 43.3 months, the 3-year PFS and OS rates were 52.4% and 60.0%, respectively. Among patients with localized disease, the 3-year PFS and OS rates were 64.5% and 67.6%, respectively. Another European study reported that the 2-year OS and PFS rates of the 28 ENKTL patients who received upfront auto-HSCT were 40% and 33%, respectively [61]. Those results were not significantly better as compared with current treatments. Thus, the major expert consensus is that consolidative auto-HSCT is not recommended in patients with localized disease when they achieve a CR with a front-line therapy [62]. For patients with advanced disease and relapsed disease, the role of auto-HSCT is unclear. Auto-HSCT could be considered for consolidation among patients who achieved complete remission, but is not in-

dicated for refractory disease or patients who fail to achieve CR.

With regard to allo-HSCT, an analysis from Japan reported the feasibility of allo-HSCT in NK/T cell lymphoma [63]. In the study including 22 patients with ENKTL, the 2-year PFS and OS rates were 34% and 40%, respectively (median follow-up, 34 mo). A multicenter analysis performed by the Asia Lymphoma Study Group reported favorable outcomes with allo-HSCT [64]. The analysis included 18 patients who underwent allo-HSCT. At a median follow-up of 21 months, the estimated 5-year PFS and OS rates were 51% and 57%, respectively. The use of L-asparaginase containing regimen (SMILE) and achieving CR prior to HSCT were the most important prognostic factors. A retrospective analysis performed by the Center for International Blood and Marrow Transplant Research reported clinical outcomes of allo-HSCT in ENKTL [65]. At a median follow-up of 36 months, the 3-year OS and PFS rates were 34% and 28%, respectively, with a non-relapse mortality rate of 30%. Recently, a retrospective analysis from Korea reported a possible role of allo-SCT in refractory/relapsed disease [66]. At a median follow-up of 28.5 months, one third (5/15) of the patients with ENKTL remained in CR after salvage allo-HSCT, although eight of them had experienced disease progression after auto-HSCT. However, since there is no clear evidence supporting allo-HSCT in ENKTL so far, the advantage of HSCT should be evaluated in each patient and further studies should be conducted to elucidate when to perform which type of HSCT in ENKTL.

NOVEL APPROACHES

The treatment outcomes of refractory/relapsed ENKTL after L-asparaginase containing regimens remain poor. In a retrospective study, with a median follow-up of 58.6 months (range, 27.9–89.2), the median second (PFS) was 4.1 months (95% CI, 3.04–5.16) and the OS was 6.4 months (95% CI, 4.36–8.51) [67]. Therefore, a new treatment approach is need-

ed for these patients.

Monoclonal antibodies

The PD-1/PD-L1 pathway is a very important checkpoint for the survival of immune mediated lysis among tumor cells. ENKTL cells are known to express abundant PD-L1 on tumor cells [68]. With this immunological background, a few checkpoint inhibitors were tested among patients with ENKTL. In a case series, seven patients with relapsed disease after L-asparaginase containing regimens (7 patients) and HSCT (2 patients) were treated with the single agent PD-L1 inhibitor pembrolizumab [69]. After a median of 7 cycles, the ORR was 100% (5 CR, and 2 PR) without significant toxicities. All the CR patients remained in CR at a median follow-up of 6 months. Another study conducted in China also recruited 7 patients with refractory or relapsed ENKTL [70]. In that study, the ORR was 57% including 2 cases of CR. One patient remained in CR after 18 cycles of pembrolizumab. Nivolumab was also tested among 3 patients with relapsed ENKTL in advanced stage [71]. All three patients responded initially, but only one patient remained in CR with 9 cycles of nivolumab. Overall, PD-L1 inhibitors showed promising responses, but the short response duration was a major limitation.

Recently, Cho *et al.* [72] proposed a new immune subtyping model that is effective in predicting the response with checkpoint inhibitors. In the model, ENKTLs were classified into four tumor immune microenvironment subgroups (immune tolerance, immune evasion-A, immune evasion-B, and immune silenced) using three immunohistochemical markers (FoxP3, PD-L1, and CD68). The response rate to pembrolizumab was 100% (1/1) in the immune tolerance group, 60% (3/5) in the immune evasion group, and 0% (0/5) in the immune silenced group. The researchers also noticed that the tumor immune microenvironment of ENKTL may change during disease progression.

CD38 is almost universally expressed within ENKTCL and high expression of CD38 predicted poor prognosis [73]. The efficacy of daratumumab, an anti-CD38 antibody, was re-

Table 2. New treatment targets for ENKTL.

Target	Treatment	Patients	Outcome	Reference
PD-1/PD-L1	Pembrolizumab	7 relapsed	5 CR, 2 PR	[69]
	Nivolumab	3 relapsed	3 CR	[71]
CD38	Daratumumab	2 RR	1 CR, 1 PR	[74, 75]
CD30	BV	2 refractory	2 CR	[79, 80]
CCR4	Mogamulizumab	Preclinical	NA	[85]
LMP1/LMP2	Autologous CTLs	11 ENKTL	9 CR	[86]
		6 active disease	4 CR	
		5 in CR	5 remained CR	
	Autologous CTLs	10 ENKTL in CR	9 remained CR	[87]
JAK/STAT	Vorinostat	1 pediatric ENKTL	CR	[89]
	Ruxolitinib	Clinical trial	Ongoing	[NCT02974647]

Abbreviations: BV, brentuximab vedotin; CR, complete remission; CTL, cytotoxic T lymphocyte; ENKTL, extranodal NK/T cell lymphoma; PR, partial remission; RR, refractory/relapsed.

ported among 2 patients with relapsed/refractory ENKTL [74, 75]. In the first case, the patient had extensively relapsed ENKTL including CSF involvement despite the previous L-asparaginase containing regimen followed by allo-HSCT. At 21 weeks of daratumumab treatment, she achieved CR with a clearance of CSF involvement. Based on this result, a multicenter phase II trial is ongoing to assess the efficacy of daratumumab in ENKTCL (NCT02927925).

The CD30 expression rate in ENKTCL is reported to be around 50–70% in different studies [76-78]. Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, induced CR in two patients with refractory ENKTL as a single agent or in combination with bendamustine [79, 80]. BV shows antitumor effect by direct killing [81], bystander effect [82], and immune augmentation effects [83]. Among them, the immune augmentation effect by BV suggests a possible combination with checkpoint inhibitors [84].

In a recent study, CCL17 and CCL22/CCR4 signaling was proposed as a strong candidate for immunotherapy against ENKTL [85]. In the study, anti-CCR4 monoclonal antibody (mogamulizumab) induced ADCC activity against NNKTL cell lines. However, further clinical study is needed to prove this concept.

Latent membrane protein (LMP)-specific cytotoxic T lymphocytes (CTL)

In a study that included 11 patients with ENKTL, autologous CTLs directed at the LMP2 or LMP1 and LMP2 antigens induced durable complete responses without significant toxicity among 52 patients with EBV-associated lymphomas [86]. Among them 6 patients had active disease during treatment. Four patients achieved CR and 3 patients remained in CR for more than 4 years. Five patients who received CTLs for consolidation remained in CR for 2–6 years.

In another study, 10 patients with ENKTL received autologous CTLs in CR after induction therapy. Eight patients had localized disease and two had advanced disease at diagnosis. With a median follow-up of 55.5 months, the 4-year OS and PFS rates were 100% and 90% (95% CI, 71.4–100), respectively [87]. Only one patient who had stage IV disease at diagnosis experienced disease relapse after 32 months. Despite the outstanding outcomes, further validation is required since the majority of the patients had localized disease where currently used combined chemotherapy and RT showed fairly good treatment outcomes without further consolidation.

Other targeted agents

Recent molecular and genetic profiling studies have deepened our understanding of the molecular biology of ENKTL, and also identified potential treatment targets, such as JAK/STAT, RUNX3, EZH2, platelet-derived growth factor, Aurora kinase, MYC, NF-κB, and NOTCH [88]. However, the clinical relevance of targeting these pathways remains to be evaluated in the future. Among them, the JAK/STAT pathway is constitutively activated in ENKTL. In a case report, a pediatric ENKTL patient with *STAT3* mutation

was successfully treated with vorinostat [89]. Vorinostat is a histone deacetylase inhibitor that has an inhibitory effect on the JAK/STAT pathway [90]. A clinical trial evaluating JAK inhibition with ruxolitinib in ENKTL is currently ongoing (NCT02974647).

CONCLUSIONS

The treatment of ENKTL has evolved rapidly in the last decade. For localized disease, current combined chemotherapy and radiotherapy cures the majority of patients. However, the treatment outcomes among patients with advanced or refractory/relapsed disease remain unsatisfactory. Recent advances in the immunotherapy and targeted therapy for ENKTL shed light on better treatment for those patients (Table 2). Future studies of promising new drugs and their combination with currently used strategies should be conducted in a collaborative way given the rarity of ENKTL.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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