Overview of the current treatment strategy in extranodal NK/T-cell lymphoma: from diagnosis to recurrence

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Abstract: Extranodal natural killer/T cell lymphoma (ENKTL) is an extraordinary subtype of non-Hodgkin's lymphoma (NHL), mainly involves the nasal cavity and the upper airway, and is influenced by the Epstein-Barr virus (EBV). Compared to other subtypes of T-cell lymphoma, ENKTL cannot be effectively treated with commonly used anthracycline-based systemic chemotherapy. Thus, the recent treatment of ENKTL has undergone significant changes based as informed by various clinical trials and prospective studies. Concurrent, sequential, and sandwich chemoradiotherapy, which is based on the alteration of the order of radiation and chemotherapy, has emerged as vital treatment approach for localized ENTKL. After the emergence of anthracycline-based systemic chemotherapy, nonanthracycline-based chemotherapy combined with L-asparaginase, including SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), Asp-MTX-Dex (L-asparaginase, methotrexate and dexamethasone), and DDGP (dexamethasone, cisplatin, gemcitabine, and peg-asparaginase) has attracted attention in advanced and relapsed/refractory (R/R) ENKTL treatment. Moreover, autologous-stem cell transplantation (auto-SCT) or allogenic stem cell transplantation (allo-SCT) has been recommended as a treatment option when patients with advanced or relapsed ENKTL achieve remission by a salvage treatment strategy. Even if ENKTL recurs, the effectiveness of immune checkpoint inhibitors (ICIs) related to programmed death-ligand 1 (PD-L1) has been proven, which is representative of the broadening of treatment options compared to many years ago. However, despite the marked improvement of therapeutic strategies in ENKTL, some patients still have dismal outcomes. Based on the understanding of the molecular and immunologic biology of ENKTL, the treatment strategy and treatment prognostic prediction model of ENKTL has been continuously evolving, treatment experience has been gradually enriched, and related data has accumulated. In this review, we discuss the current and emerging treatments for early or advanced relapsed or refractory ENKTL.

Keywords: Extranodal natural killer/T cell lymphoma (ENKTL); L-asparaginase; concurrent chemoradiotherapy (CCRT); immune checkpoint inhibitor (ICI)

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Background

Extranodal natural killer (NK) T-cell lymphoma (ENKTL) is a singular non-Hodgkin’s lymphoma (NHL) that primarily involves the nasal cavity and nasopharynx and can be affected by the Epstein-Barr virus (EBV) (1). Before the year 2000, most treatments were based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy or radiation alone (2). However, the outcomes from these treatments were dismal. In the era of (CHOP)-based chemotherapy, the prognosis was grim...
for most patients, with a 5-year overall survival (OS) of 30–40%. Even in the patients with limited-stage ENKTL, the 5-year progression-free survival (PFS) and OS of ENKTL was about 44% and 21% respectively. Moreover, the 5-year OS to the treatment of newly diagnosed advanced ENKTL was lower than 30%, and that of relapsed or refractory ENKTL was worse (3-5).

Recently, the treatment of ENKTL has undergone significant changes. Concurrent or sequential chemoradiotherapy has emerged as a vital treatment option for localized ENKTL, and nonanthracycline-based chemotherapy combined with L-asparaginase is drawing attention in advanced ENKTL treatment. Studies have shown that localized ENKTL can maintain long-term efficacy, with a 2-year OS of 88% and a 5-year OS of 65% (6,7). Also, patients with advanced-stage or relapsed/refractory ENKTL were found to obtain excellent extended survival results with a response rate of 70–80% and a 2-year PFS or OS of approximately 40% (8,9). Furthermore, the efficacy of the anti–programmed cell death protein 1 (PD-1) antibody (pembrolizumab, nivolumab, sintilimab) and anti–programmed death-ligand 1 (PD-L1) antibody (avelumab, CS1001) was reported for cases that failed previous systemic chemotherapy (10-12). However, experience concerning anti-PD-1 antibody and anti-PD-L1 antibody efficacy administered to patients with relapsed/refractory ENKTL is still lacking. Therefore, any significant improvements in clinical outcomes in daily practice in ENKTL patients have been achieved through use of a prospective registry (13).

Nevertheless, some patients with ENKTL still do not have satisfactory prognoses. Consequently, researchers have developed a prognostic index of natural killer lymphoma (PINK)/PINK-E (EBV) and central nervous system (CNS)-PINK. With objective and weighted scoring systems, we can segment the treatments applied to patients and predict their prognosis more accurately (14,15). Other studies have noted that the effect of immunotherapy is not the same in all ENKTL patients, and the difference in efficacy is based on the discrepancy in the tumor microenvironment, and applying immunotherapy that considers these tumor microenvironments has been recommended (16,17).

As described above, the treatment strategy and prognostic prediction model of ENKTL have continued to evolve, treatment experience has gradually been enriched, and related data have accumulated. To provide an account for these changes, we review the treatment options in the localized, advanced, and relapsed settings and discuss the factors to be considered in creating a plan for future patient care.

**Why novel treatment strategies in ENKTL are drawing attention**

Radiotherapy is an important treatment method in localized ENKTL, so the appropriate dose, clinical target volume (CTV), and radiotherapy delivery method have continued to develop (8). However, there is concern that radiotherapy alone is insufficient to reduce the rate of local failure, regional failure, and systemic disease recurrence (18,19). Several key approaches with combination radiation and chemotherapy (concurrent, sequential, and sandwich) for the locoregional disease have emerged.

Studies have found that CHOP combined with radiotherapy does not produce an effective survival outcome compared to radiotherapy alone (2,20,21) because of the high expression of P-glycoprotein, resulting in tumor multidrug resistance to anthracycline (22). Moreover, in vitro analysis to compare drug efficacy between L-asparaginase and anthracyclines demonstrated that L-asparaginase administration in NK-cell leukemia/lymphoma cell lines has moderate antitumor effect due to the decreased ability of asparagine synthesis in tumor cells; as a result, L-asparaginase has garnered attention as an essential therapeutic agent in ENKTL. Overall, radiotherapy and nonanthracycline with L-asparaginase have become the strategic treatments of localized and advanced ENKTL (23).

**Treatment strategies for newly diagnosed patients with localized ENKTL**

The current form of chemoradiotherapy, which we currently use for localized ENKTL, is based on previous failures. Its administration can be divided into 4 variations: simultaneous chemoradiotherapy, radiotherapy followed by chemotherapy, chemotherapy followed by radiotherapy, and sandwich chemoradiotherapy (Table 1).

In one Japanese phase I/II study, 3 courses of 2/3 DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) were administered for 5–6 weeks simultaneously. This concurrent chemoradiotherapy (CCRT) strategy yielded a 78% overall response rate (ORR), a 67% 2-year PFS, and 78% 2-year OS (24). Another study applied adjuvant CCRT with weekly cisplatin with radiation followed by VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) and
yielded an ORR of 80%, a 3-year PFS of 85%, and a 3-year OS of 86%. This finding was similar to treatment results of DeVIC-based CCRT (25); however, this treatment scheme took more than 14–16 weeks to complete. Another phase II study conducted CCRT followed by chemotherapy with L-asparaginase (VIDL, etoposide, ifosfamide, dexamethasone, and L-asparaginase) (26). This approach shortened the treatment period slightly (11-13 weeks) and achieved similar therapeutic efficacy.

When it is too challenging to secure radiotherapy margin for patients with localized ENKTL, or it is impossible to wait for the time required to simulate radiotherapy, sequential chemotherapy followed by radiotherapy may be a viable option. Therapies that have proven effective in clinical researches include SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), modified SMILE, and DICE-L (cisplatin, ifosfamide, etoposide, dexamethasone, and L-asparaginase) (27,29).

Depending on the regimen, the potency is similar, but there is a difference in the incidence of adverse events (AEs), so it is necessary to consider the age, performance, and comorbidities of the individual.

Sandwich chemoradiotherapy comprises sequential chemoradiotherapy followed by additional chemotherapy. A prospective study was conducted to appraise the efficacy and toxicity of the treatment scheme consisting of GELOX (gemcitabine, oxaliplatin, and L-asparaginase) followed by radiotherapy, and then GELOX again (28). This yielded an excellent ORR (96%) and 2-year PFS (86%), with only a few grade 3 or 4 AEs occurring. The researchers recommended that sandwich chemoradiotherapy containing GELOX can be a practical and feasible treatment strategy for localized ENKTL.

The Asian Lymphoma Study Group analyzed an international cohort of patients with newly diagnosed stage I/II ENKTL to evaluate the efficacy and safety of CCRT and sequential chemotherapy followed by radiotherapy. The results indicated no difference in the response and survival results between the chemoradiotherapy types (30).

Based on the findings of previous trials, we can conclude that chemotherapy combined with radiation is essential. A recent prospective cohort study confirmed these observations. Fox et al. showed a definite survival benefit for chemoradiation (3-year OS, 70%) against chemotherapy alone (3-year OS, 12%) in patients with localized ENKTL (13). In addition to the application of a therapeutic concept for localized ENKTL, numerous clinical trials evaluating new chemoradiotherapy combinations are

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Chemoradiotherapy for localized ENKTL</th>
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<tr>
<td>Planned treatment scheme</td>
<td>Total radiation (dose/duration)</td>
</tr>
<tr>
<td>CCRT</td>
<td>50 Gy/5–6 weeks, without cisplatin</td>
</tr>
<tr>
<td>CCR-CT</td>
<td>40–52.8 Gy/3–5 weeks, without cisplatin</td>
</tr>
<tr>
<td>CCR-CT</td>
<td>40–44 Gy/3–5 weeks, with cisplatin</td>
</tr>
<tr>
<td>CT-RT</td>
<td>45 Gy, without cisplatin, mSMILE/1-2 cycles</td>
</tr>
<tr>
<td>CT-RT-CT</td>
<td>56 Gy, without cisplatin</td>
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</tbody>
</table>

CCRT, concurrent chemoradiotherapy; CT, chemotherapy; ORR, overall response rate; CR, complete response; PR, partial response; AE, adverse event; PFS, progression-free survival; OS, overall survival; NR, not reached; NA, no assessment; Ref, reference.
continuously being performed. The recent clinical trials for localized ENKTL are summarized in Table 2.

**Treatment strategies for patients with advanced ENKTL (Table 3)**

Recently, CHOP or CHOP-like chemotherapy has been discontinued. The chemotherapy regimens most frequently used in clinic are SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), VIDL (etoposide, ifosfamide, dexamethasone, and L-asparaginase), MIDLE (methotrexate, ifosfamide, dexamethasone, L-asparaginase, and etoposide), and DDGP (dexamethasone, cisplatin, gemcitabine, and L-asparaginase) (13). In a phase I and II study of a SMILE regimen for newly diagnosed advanced or R/R ENKTL (31-33,37), the ORR after 2 SMILE cycles were approximately 80%, and the 1-year OS and PFS were 55% and 53%, respectively. Although there were no subsequent treatment-related deaths, grade 3 or 4 neutropenia (92%) and infection (16%) were common. Unexpectedly, the allergic reaction caused by L-asparaginase was manageable, and the chemotherapy did not stop due to hypersensitivity. Thus, researchers recommended the need for rigorous monitoring of myelosuppression and infection during and after SMILE.

In a French phase 2 study, a cohort of 19 patients who received AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) had an ORR of 78%, and a 2-year PFS and OS of both about 40%. Furthermore, grade 3 or 4 neutropenia developed after chemotherapy in 42% of patients (35).

Gemcitabine has shown substantial efficacy according to a retrospective study (38); therefore, the gemcitabine and L-asparaginase-based chemotherapy regimen, DDGP has been further developed. In a retrospective study to evaluate the efficacy and safety of DDGP, 28 patients with stage III or IV ENKTL who received DDGP showed an ORR of 89.3%, a 2-year PFS of 68.4%, and a 2-year OS of 84.5% (35). A randomized trial for newly diagnosed advanced ENKTL was performed to compare the efficacy and survival of DDGP versus those of the SMILE regimen (36). The ORR (90% vs. 60%), 3-year PFS rate (56.6% vs. 41.8%), and 5-year OS rate (74.3% vs. 51.7%) in the DDGP group were superior to those of the SMILE group, while, grade 3 or 4 leukopenia, neutropenia, and mucositis were significantly higher in the SMILE group. Moreover, treatment-related mortality was about 17.5% in the SMILE group and 10% in the DDGP group. Researchers thus emphasized the prolonged survival, better tolerability, and superior safety of the DDGP regimen in newly diagnosed stage III or IV ENKTL patients. Kwong et al. also pointed out the same shortcomings of SMILE therapy, including a high incidence of grade 3 or 4 hematologic AEs (67%) (32). Among 87 patients who were given SMILE, death from severe infections only occurred in 5 patients (6%). However, the sample size was not sufficiently large to determine which chemotherapy regimen is better. Therefore, although the priority of regimens for advanced-stage or R/R ENKTL remains controversial, the common opinion based on current data suggest that the treatment scheme of advanced-stage ENKTL should consist of non-MDR-dependent drugs with L-asparaginase.

**Treatment strategies for patients with R/R ENKTL**

Patients with advanced and R/R ENKTL have poor outcomes. Therefore, many clinicians have performed high-dose chemotherapy with hematopoietic stem cell transplantation. In a retrospective study in 2008, Lee et al. reported the outcome of autologous stem cell transplantation (auto-SCT) in 59 patients with ENKTL. With a median follow-up of 116.5 months, the median survival was not reached for the auto-SCT group, but it was 43.5 months for the patients who did not receive auto-SCT. Also, the authors emphasized that the disease status of the auto-SCT patients was more significantly influenced by disease-specific survival (39). Another retrospective study that estimated the efficacy of auto-SCT noted that achieving complete response (CR) before auto-SCT was the only significant prognostic factor (40). Kim et al. assessed the efficacy and safety of induction treatment with SMILE and consolidation with upfront auto-SCT. Among 27 patients with advanced-stage ENKTL, only 11 patients underwent auto-SCT, and there was no transplantation-related mortality (TRM) (33). However, the role of auto-SCT for patients with advanced ENKTL has not yet been established clearly, due to the fact that ENKTL frequently recurs during or after induction treatment.

There is also no consensus opinion regarding performing allogeneic stem cell transplantation (allo-SCT) for advanced or relapsed ENKTL patients. In Japan, the retrospective data of 28 NK cell neoplasm patients who underwent allo-SCT were reviewed. With a median follow-up of 34 months, the 2-year PFS and OS were 34% and 40%,
respectively. However, the incidence of acute and chronic graft-versus-host disease (GVHD) was estimated at 43% (12/28) and 28% (8/28), respectively, with the TRM being 28% (8/28) (41). In another retrospective study that reviewed 12 patients with ENKTL who received allo-SCT, the 3-year event-free survival (EFS) and OS were 53% and 55%, respectively. All-grade acute GVHD was observed in 50% (6/12) of the patients, and atypical infections, such as cytomegalovirus, adenovirus, and BK virus, were also recorded in 50% (6/12) of the patients (42). Given these results, it is still questionable whether the benefits of allo-SCT outweigh the costs. Thus, the role of transplantation in ENKTL treatment remains ambiguous due to the limited data. However, auto-SCT or allo-SCT can be considered when patients with advanced or relapsed ENKTL achieve remission by salvage treatment strategy.

One study found that patients who relapsed after being treated with L-asparaginase-containing regimens received only a few months of survival (43). Gene expression profiling data has established that the expression of JAK/STAT pathway genes is higher in ENKTL cells than in normal NK cells (44). Song et al. conducted a study to determine the relationship between JAK/STAT mutation and PD-L1 expression (45). Oncogenic activation of the

<table>
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<tr>
<th>Table 2 Ongoing clinical trials of new chemotherapy combinations for newly diagnosed or relapsed or refractory ENKTL</th>
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<tr>
<td>Intervention/treatment</td>
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<tr>
<td>-------------------------</td>
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<tr>
<td>Newly diagnosed</td>
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<tr>
<td>Chidamide ± GDP</td>
</tr>
<tr>
<td>GELAD</td>
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<tr>
<td>IPGDP</td>
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<tr>
<td>Anti-PD-1 mAb (sintilimab) + pegaspargase</td>
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<tr>
<td>Anti-PD-1 mAb (toripalimab) + P-GemOx</td>
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<tr>
<td>Anti-PD-1 mAb (pembrolizumab) + pegaspargase + chidamide</td>
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<tr>
<td>Pegasparagase-COEPT</td>
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<tr>
<td>Anti-PD-1 mAb (sintilimab) + P-GemOx</td>
</tr>
<tr>
<td>Relapse/refractory</td>
</tr>
<tr>
<td>ICE + ATG-101 (Selinexor) vs. GEMOX + ATG101 (Selinexor)</td>
</tr>
<tr>
<td>Chidamide + etoposide</td>
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<tr>
<td>Copanilisib + gemcitabine</td>
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<tr>
<td>Ruxolitinib</td>
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<tr>
<td>Anti-PD-1 mAb (sintilimab) + lenalidomide</td>
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<tr>
<td>Anti-PD-1 mAb (sintilimab) + decitabine</td>
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<tr>
<td>Anti-PD-1 mAb (SHR-1210)</td>
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<tr>
<td>Anti-PD-1 mAb (pembrolizumab)</td>
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<tr>
<td>Anti-PD1/PD-L1 bispecific antibody (IBI318)</td>
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<tr>
<td>Anti-PD-L1 mAb (IMC-001)</td>
</tr>
</tbody>
</table>

IMRT, definitive intensity-modulated radiotherapy; CT, chemotherapy; RT, radiotherapy; mAb, monoclonal antibody; GDP, gemcitabine, dexamethasone, prednisolone; GELAD, gemcitabine, etoposide, dexamethasone, pegaspargase; IPGDP, ifosfamide, pegaspargase, gemcitabine, cisplatin, dexamethasone; COEP, pegaspargase, cyclophosphamide, vincristine, etoposide, prednisone; P-GemOx, pegaspargase, gemcitabine, and oxaliplatin; GPED, gemcitabine, pegaspargase, etoposide, dexamethasone; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
Table 3 Chemotherapy for advanced ENKTL

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>No.</th>
<th>Response, % (CR+PR)</th>
<th>Grade 3/4 AE</th>
<th>PFS</th>
<th>OS</th>
<th>Ref</th>
</tr>
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<tbody>
<tr>
<td>SMILE</td>
<td>38</td>
<td>79% (17 CR+13 PR)</td>
<td>Leucopenia: 100%</td>
<td>1-year PFS: 53%</td>
<td>1-year OS: 55%</td>
<td>(31)</td>
</tr>
<tr>
<td>SMILE</td>
<td>43</td>
<td>84% (28 CR+8 PR)</td>
<td>Neutropenia: 45%, TRM: 7%</td>
<td>4-year DFS: 60%±22.9%</td>
<td>5-year OS: 49.9%±12.5%</td>
<td>(32,33)</td>
</tr>
<tr>
<td>SMILE</td>
<td>27</td>
<td>59% (9 CR+7 PR)</td>
<td>Cytopenia: 9.3%, TRM: 12%</td>
<td>Median PFS: 5.1 months</td>
<td>Median OS: 10.6 months</td>
<td>(33)</td>
</tr>
<tr>
<td>Asp-MTX-Dex</td>
<td>19</td>
<td>78% (11 CR+3 PR)</td>
<td>Leucopenia: 44%</td>
<td>2-year PFS: 40%</td>
<td>2-year OS: 40%</td>
<td>(34)</td>
</tr>
<tr>
<td>DDGP</td>
<td>28</td>
<td>89.3% (17 CR+8 PR)</td>
<td>NA</td>
<td>2-year PFS: 68.4%</td>
<td>2-year OS: 84.5%</td>
<td>(35)</td>
</tr>
<tr>
<td>SMILE vs. DDGP</td>
<td>40 vs. 40</td>
<td>90% vs. 60% (27 CR+9 PR) vs. (19 CR+5 PR)</td>
<td>Leucopenia: 62.5% vs. 85%, mucositis: 0% vs. 12%, TRM: 0% vs. 17.5%</td>
<td>3-year PFS: 56.6% vs. 41.8%</td>
<td>5-year OS: 74.3% vs. 51.7%</td>
<td>(36)</td>
</tr>
</tbody>
</table>

No., number of patients; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; DDGP, dexamethasone, cisplatin, gemcitabine, and peg-asparaginase; ORR, overall response rate; CR, complete response; PR, partial response; AE, adverse event; TRM, treatment-related mortality; PFS, progression-free survival; DFS, disease-free survival; OS, overall survival; NA, no assessment; Ref, reference.

STAT3 pathway showed a high prevalence of about 21% in ENKTL cases. Moreover, activated STAT3 was found to affect PD-L1 expression by strongly binding to the promoter site of the PD-L1 gene. The use of anti-PD-1 antibodies (pembrolizumab, nivolumab, and sintilimab) or anti-PD-L1 antibodies (avelumab and CS1001) can thus interrupt PD-L1 and PD-1 interaction enabling host immune surveillance (Table 4).

Wong et al. retrospectively analyzed the outcomes of anti-PD-1 antibody administration in R/R ENKTL lymphomas after L-asparaginase combination chemotherapy. All 7 patients (100%) included in the study obtained an objective response (10). However, another retrospective study reported that pembrolizumab could only yield an ORR of 44% (6/14) (47). For nivolumab, Chan et al. indicated that, similar to pembrolizumab, the smallest available dose is also useful for R/R ENKTL; although this outcome was reported in only 3 patients, nivolumab showed less toxicity and 100% response in relapsed ENKTL cases (48). A multicenter, single-arm, phase II study examined the efficacy of another anti-PD-1 antibody, sintilimab, in R/R ENKTL patients: 28 patients were treated with about 3 cycles (range, 1–13) of sintilimab. The ORR, including the number of patients with CR and partial response (PR), was 68% (19/28) (49).

Kim et al. assessed the efficacy and safety of treatment with anti-PD-L1 antibody (avelumab) in R/R ENKTL. A total of 21 patients were administrated 10 mg/kg of avelumab every 4 weeks. The ORR was 38%, with CR achieved in 24%. Based on the results showing a significant response to immunotherapy in patients with high expression of PD-L1, the expression of PD-L1 in tumor tissue has been considered critical for predicting response (12). Furthermore, the efficacy and safety of CS1001, another PD-L1 monoclonal immunoglobulin reported by a phase II clinical trial, has yielded an appreciable response rate and durable response duration without severe toxicities (11,50).

Although the efficacy of immune checkpoint inhibitors (ICIs) on ENKTL has been reported on several occasions, the correlation of PD-L1 expression to therapeutic efficacy remains controversial. Therefore, many researchers have speculated using the relationship between tumors and their surrounding tumor immune microenvironment (TIME) as a valuable tool in predictions. Somasundaram et al. developed 4 categories of TIME for ENKTL by applying immunohistochemistry (IHC) and gene expression. They defined the depletion of effector T cells around the tumor as immune silencing (IS) and predicted a decrease in the effectiveness of immunotherapy in patients with the IS type (51). In a multi-omics study, Xiong et al. identified the molecular subtypes of ENKTL based on the RNA helicase family, tumor suppressors, the JAK-STAT pathway, epigenetic modifiers, and the RAS-MAPK pathway (17). They recommended choosing a PD-1 blocker while also considering NK cell-associated immunity and the PD-L1 marker. Lim et al. conducted a genetic analysis study on tumor tissues from 19 patients with R/R ENKTL. Using genetic profiling, they found that PD-L1 structural rearrangements are more useful than PD-L1 as a biomarker to predict the response to ICI (52).
Based on these findings, we believe that treatment strategies should factor in genetic alterations, as well as the molecular and cellular interactions related to EBV-associated lymphomagenesis, before the initiation of immunotherapy. However, the limitation of these technical methods is that these testing techniques are not used widely and are not accessible in general clinics.

Although a diversity of research streams have enhanced our understanding of the disease aspects and therapeutic strategies of ENKTL over the past decade, treatment limitations still exist in advanced and R/R ENKTL cases. Fortunately, various clinical trials currently are being conducted with the aim of evaluating the efficacy and safety of chemotherapies or ICIs for advanced or R/R ENKTL patients (Table 2).

### Criteria for CNS prophylaxis intervention in ENKTL patients

According to the previous studies, 0% to 6% of patients with ENKTL have experienced CNS recurrence (53,54). Although the incidence of CNS disease in ENKTL is low, the means for prognosis is inferior, and more attention is needed to improve this.

Kim *et al.* conducted developed a model to predict CNS events in 253 ENKTL patients (14). Using to Cox regression analyses, they established a CNS prognostic index of natural killer lymphoma (CNS-PINK) composed of 2 risk groups: 0 or 1 point was considered low risk while 2 points was considered high risk (PINK group III/IV or extranodal involvement; Table 3). It was found that the incidence of CNS recurrence increased to 22.8% in the CNS-PINK high-risk group. Additionally, among patients categorized into the high-risk group, patients who were administered S-ID-MTX presented a lower rate of CNS recurrence than patients who were not. However, there was no difference in CNS recurrence according to S-ID-MTX in patients classified in the low-risk group. Based on these findings, the authors recommended considering active CNS prophylaxis of patients with a high-risk CNS-PINK (15).

### Conclusions

Chemotherapy combined with radiation should be recommended as standard care for localized ENKTL patients regardless of the sequence. Different chemotherapy regimens for localized ENKTL show no significant differences in efficacy, but the specifics of the patient’s...
condition should be included into the treatment plan to account for potential AEs. For advanced-stage ENKTL, systemic chemotherapy, including L-asparaginase, is regarded as the front-line treatment. Immunotherapy is also effective in advanced or R/R ENKTL, but there are no significant biomarkers to predict treatment efficacy. Thus, further research concerning the EBV-related tumor microenvironment is needed to identify new predictive biomarkers of immunotherapy, while studies for developing prognostic tools for ENKTL should be continuously conducted.

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