# Chapter 10
# Extranodal NK/T-Cell Lymphoma

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## Background and Clinical Presentation

### *Introduction and Epidemiology*

Extranodal NK/T-cell lymphoma (ENKTCL) is a rare, aggressive form of non-Hodgkin lymphoma which occurs worldwide but is more common in Asia and Central and South America. In countries such as China, Japan, and Brazil, ENKTCL accounts for 5–15% of all lymphoma cases [1]. However, in the United States and Europe, it accounts for less than 1% of all lymphoma cases [2]. ENKTCL is further divided into subtypes based on location of disease. The nasal type is the most common and frequently presents with localized disease. Sites most commonly involved include the nose, nasopharynx, oropharynx, and Waldeyer's ring; fewer than 20% of cases present with extra-nasal lesions [3]. Dissemination to sites such as the bone marrow, spleen, liver, and skin with peripheral blood involvement is considered advanced stage disease.

The immunophenotype of ENKTCL is unique, with most cases expressing NK-cell markers (CD2+, cytoplasmic CD3+, and CD56+) (Fig. 10.1). Tumor cells are almost always infected by Epstein-Barr virus (EBV), which can be detected by in situ hybridization for EBV early RNA (EBER). The malignant cells may also express perforin, granzyme B, or TIA-I. In rare cases, CD56 is negative, and in exceptionally rare cases, T-cell gene rearrangement is positive. These cases are included under the "T-cell" nomenclature of NK/T-cell lymphoma.

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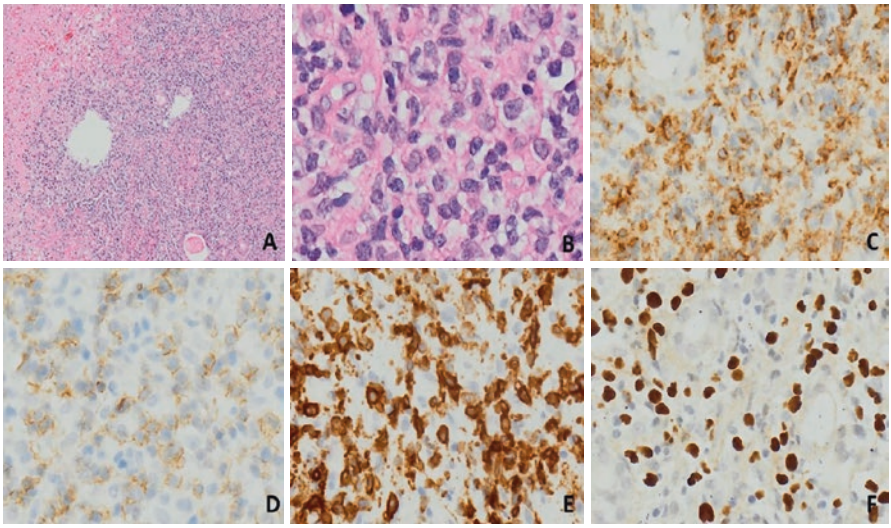


**Fig. 10.1** (**a**) H&E, low-power view of the nasal septum biopsy with diffuse lymphoid infiltrate, entrapped epithelium, and areas of necrosis (top left); (**b**) H&E, high-power view of atypical lymphoid cells with intermediate-sized, irregular nuclei; (**c**) CD43 expression is present in the neoplastic lymphoid population; (**d**) CD56 is also expressed in the neoplastic lymphocytes; (**e**) CD3 highlights background mature T cells while sparing the neoplastic NK/T-cell infiltrate; (**f**) In situ hybridization for Epstein-Barr virus-encoded RNA is positive. (Imaging courtesy of Robert K. McCall, MD. Vanderbilt University Medical Center)

## *Clinical Presentation*

ENKTCL is a primarily an extranodal disease, most often presenting as a localized lymphoma in the nasal region. Lesions may occur in the nose, nasopharynx, paranasal sinuses, tonsils, Waldeyer's ring, or oropharynx. Spread to the cerebrospinal fluid is rare [1]. Symptoms may include epistaxis, obstruction, and pain from necrotic lesions in the nose or hard palate. Patients may also present with extra-nasal masses of the skin, salivary glands, testis, and gastrointestinal tract. Positron emission tomography (PET) imaging has demonstrated that most extra-nasal lymphomas are associated with occult nasal primary tumors. This implies that the extra-nasal subtypes are likely disseminated nasal lymphomas. To meet the formal definition of extra-nasal ENKTCL, the absence of a nasal primary mass must be detected by random nasopharyngeal biopsies and PET imaging. Rarely, patients present with widespread disease. If there is involvement of the bone marrow and peripheral blood, the diagnosis can overlap with aggressive NK-cell leukemia. NK-cell leukemia carries an extremely poor prognosis, with a median survival of weeks [4].

The differential diagnosis for ENKTCL includes malignant and nonmalignant conditions such as invasive fungal and bacterial infections, Wegener's granulomatosis, NK-cell enteropathy, enteropathy-associated T-cell lymphoma, other lymphomas, and primary and secondary malignancies. Among these considerations,

NK-cell enteropathy is particularly difficult to differentiate from ENKTCL due to similar pathologic findings. Patients with NK-cell enteropathy classically have a CD56 and cytoplasmic CD3-positive infiltrate which mimics ENKTCL. EBV testing in NK-cell enteropathy, however, is negative which excludes the diagnosis of ENKTCL. Mansoor et al. published a case series in which eight patients with NK-cell enteropathy were misdiagnosed with ENKTCL. Several received unnecessary chemotherapy as a result [5]. This report highlights the challenges and diagnostic overlap between these conditions. Unlike ENKTCL, in patients with NK-cell enteropathy, the disease is limited to the gastrointestinal tract. Given the immunophenotypic overlap, it is important to work closely with pathologists to confirm ENKTCL before initiating aggressive therapy [5].

## *Initial Evaluation, Diagnosis, and Staging*

Patients suspected of having ENKTCL should undergo a thorough initial evaluation to include nasal panendoscopy, PET/CT imaging, and plasma EBV DNA testing. Nasal panendoscopy should be performed regardless of the primary site of presentation, and random biopsies should be taken even if no suspicious lesions are seen. Biopsies should include the leading edges of the lesions because biopsy specimens are often necrotic [6]. Diagnostic delays can compromise overall survival by increasing the likelihood of disease dissemination in the interim. In one study of 25 patients with ENKTCL, the median time from symptoms to diagnosis was 5 months. Twelve patients required more than one diagnostic biopsy; delay in diagnosis was prolonged up to 36 months. Given these concerns, generous biopsy specimens should be taken when feasible to ensure more timely diagnoses [2].

Upon diagnosis, the first important distinction is whether the specimen is surface or cytoplasmic CD3 positive. If a fresh specimen is not sent, the next step is to confirm positive results on CD56, EBER (EBV by in situ hybridization), and cytotoxic molecule testing. Cytologic examination will reveal small- to medium-sized cells with azurophilic granules and pale cytoplasm. Neoplastic cells are often mixed with lymphocytes, plasma cells, and eosinophils. Thus, the term "polymorphic reticulosis" is used to describe the histology of ENKTCL. Tumor cells are classically positive for CD2, cytoplasmic CD3, and CD56.

Next-generation sequencing has identified several somatic mutations in the Janus kinase 3 (JAK3) gene leading to constitutive activation of the JAK/STAT pathway. In this scenario, increased cell growth occurs in approximately 35% of cases [7]. The most frequent cytogenetic aberration in NK malignancies is the deletion of chromosome 6q21. Notable tumor suppressor genes in this region include FOXO3, PRDM1, and HACE1. PRDM1 is integral to the maturation and homeostasis of NK cells [8]. In addition to the JAK/STAT pathway, other activated pathways resulting in tumorigenesis include AKT, Wnt, and Notch-1.

Initial imaging should include PET/CT, as lesions are invariably PET avid [9]. The SUV maximum for ENKTCL is lower than for other aggressive lymphomas

such as diffuse large B-cell lymphoma. As in other types of non-Hodgkin lymphoma, the Ann Arbor System is used for staging. Plasma EBV DNA testing should be performed at diagnosis and can be serially monitored to follow response to treatment and to detect recurrence [10].

## *Conventional Treatment Approach for Localized Nasal-Type ENKTCL*

Treatment approaches are based on subtype (nasal or extra-nasal disease) and stage (localized or advanced). For patients with stage I/II nasal-type ENKTCL who are candidates for chemotherapy, standard treatment options include chemoradiation given either in concurrent, sequential, or "sandwich" fashion defined as induction chemotherapy followed by radiation and then consolidation chemotherapy.

### *Concurrent Chemoradiation*

Evidence for concurrent chemoradiation stems from two prospective trials. Kim et al. conducted a study using concurrent radiation therapy (40 Gy) and cisplatin followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) in patients with localized nasal NK/T-cell lymphoma. The overall response rate was 83%, and the complete response rate was 80%. Patients in this study had a 3-year overall survival of 86% and a 3-year progression-free survival of 85% [11]. In 2009, Yamaguchi et al. conducted a trial in localized nasal type using concurrent radiation therapy (50 Gy) and DeVIC chemotherapy (dexamethasone, etoposide, ifosfamide, and carboplatin). The overall response rate was 81%, and 77% of the 27 patients achieved a complete response. The 5-year overall survival rate was 70%, and the 5-year progression-free survival rate was 63%. Grade 3/4 neutropenia occurred in 93% of patients and grade 3 radiation-related mucositis in 30% of patients [12].

### *Sandwich Chemoradiation*

Sandwich chemoradiation was efficacious in two studies of NK/T-cell lymphoma. Jiang et al. conducted a phase II trial of 26 patients with stage I/II nasal disease. Patients received six cycles of L-asparaginase, vincristine, and prednisolone (LVP) sandwiched with radiation therapy after two cycles. After completion of radiation therapy and 2–4 cycles of LVP, the ORR was 89%, and the CR rate was 81%. The 2-year OS was 88.5%, and 2-year PFS was 80.6%. Grade 3 neutropenia occurred in 2.7% of patients, and grade 3 radiation-related mucositis was seen in 23.1% of patients [13]. In another prospective trial, gemcitabine, L-asparaginase, and

oxaliplatin (GELOX) were given for two cycles followed by radiation therapy (56 Gy). After radiation, GELOX was given for 2–4 more cycles. The overall response rate was 96%, and the complete remission rate was 74%, with a 2-year overall survival rate of 86%. Grade 3/4 neutropenia occurred in 33.3% and radiation-related mucositis in 15% of participants [14].

### *Sequential Chemoradiation*

In a retrospective review, Lunning et al. described their experience with a modified SMILE chemotherapy regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide). In this regimen, one dose of L-asparaginase is given, rather than a dose with each cycle. Twelve patients with stage I nasal-type ENKTCL received two cycles of modified SMILE followed by 45 Gy of radiation therapy. Patients with stage II disease received three cycles followed by radiation therapy. After 1–2 cycles of the modified SMILE regimen, the overall response rate was 92%, and the complete response rate was 75% [15].

## *Radiation Therapy for Localized Nasal-Type ENKTCL*

For patients with localized, nasal-type ENKTCL, radiation therapy is an integral component of treatment. In 2017, Yang et al. evaluated 1332 patients with localized ENKTCL treated at ten institutions between 2000 and 2014. The goal of the study was to determine if improved locoregional control translates into progression-free and overall survival gains for patients with early stage disease. Patients received radiation, chemotherapy, or combination chemoradiation. After analysis, it was found that radiation therapy had a dose-dependent effect on locoregional control, PFS, and OS. High-dose radiation therapy, defined as ≥50 Gy, led to improved locoregional control (85% vs 73%), PFS (61% vs 50%), and OS (70% vs 58%) [16]. The LRC benefit with radiation therapy in the high-dose group was independent of the sequence of chemotherapy relative to radiation therapy and was independent of response to chemotherapy. This study concluded 50 Gy is the optimal dose, and the gains in PFS and OS highlight the significant role of radiation therapy in the treatment of early stage disease. The technique of radiation therapy delivery has also changed significantly in recent years, with most institutions using intensity-modulated radiation therapy (IMRT) to improve target coverage and reduce dose to adjacent normal tissues improving toxicity outcomes [17, 18].

The benefit of chemoradiotherapy as compared to radiation therapy alone has also been investigated in past studies with conflicting results. In 2009, Ma et al. conducted a study of 64 patients with stage IE or IIE early stage ENKTCL. Of these patients, 23 received radiation therapy alone, and 41 received chemoradiation with an anthracycline-based regimen. The 5-year OS rate was 57.9% for those who

received radiation therapy alone and 61.5% for those who received chemoradiation ($P = 0.47$). The study concluded that chemoradiation compared to radiation therapy alone did not lead to improved OS. Of note, anthracycline-based regimens have been proven to be inferior to asparaginase-based chemotherapy and represent an important limitation of this study [19].

A more recent study conducted by Su et al. reviewed 248 patients in the United States with localized disease from 2004 to 2014. Chemoradiation was given in 68.9%, and radiation therapy alone was given in 31.1%. After multivariable analysis, chemoradiation was associated with an improved OS compared to radiation therapy alone with a hazard ratio of 0.504. The survival benefit was also apparent in the geriatric subgroup. Based on this and other studies, the preferred approach endorsed by the NCCN is to recommend chemoradiation for patients who are fit to receive chemotherapy [20].

## *Summary of Treatment Recommendations for Localized Nasal Type*

The decision of which regimen to use (concurrent vs. sandwich vs. sequential chemoradiotherapy) can be challenging, and various factors including adherence must be accounted for. The logistics of performing concurrent chemoradiotherapy make this a difficult treatment strategy in some patients with limited transportation. One advantage of the sequential approach is that radiation therapy is often better tolerated, as patients are more likely in a complete response. Ultimate treatment decisions must be made individually. If a patient is deemed not to be fit for chemotherapy, radiation therapy alone is a viable option for localized nasal-type ENKTCL. Treatment options are summarized in Table 10.1.

## *Conventional Treatment Approach for Extra-Nasal Type ENKTCL*

The presence of extra-nasal disease is considered a poor prognostic factor, and patients with this subtype generally have a more difficult course. This impacts treatment recommendations, which tend to favor more aggressive regimens compared to those outlined for localized nasal-type disease. Many past studies that included patients with localized extra-nasal disease were performed before PET/CT imaging. These cases were likely to include patients with nasal primary tumors, so the results are difficult to interpret. There is a definitive association between extra-nasal disease and decreased overall survival [1]. Therefore, for all stages of extra-nasal-type ENKTCL, asparaginase-based systemic chemotherapy is recommended. Radiation therapy may be indicated, depending on the site of disease [6].

**Table 10.1** Summary of treatment recommendations [12–16]

| Concurrent chemoradiation | | |
|---|---|---|
| Treatment | Number treated | Survival rates % |
| Cisplatin 30 mg/m$^2$ weekly with radiation (40 Gy) followed by [a]VIPD × 3 cycles | 30 | 3 year PFS – 85 |
| | | 3 year OS – 86 |
| [b]DeVIC chemotherapy × 3 cycles with radiation (50 Gy) | 33 | 2 year OS – 78 |
| Sandwich chemotherapy | | |
| Treatment modality | Number treated | Survival rates |
| [c]LVP × 2 cycles followed by radiation (56 Gy) then LVP for 2–4 cycles | 26 | 2 year PFS – 80.6 |
| | | 2 year OS – 88.5 |
| [d]GELOX × 2 cycles followed by radiation (56 Gy) then GELOX × 2–4 cycles | 27 | 2 year PFS and OS – 86% |
| Sequential chemoradiation | | |
| [e]Modified SMILE × 2–3 cycles followed by radiation (45 Gy) | 12 | ORR – 92 |

*PFS* progression-free survival, *OS* overall survival, *ORR* overall response rate

[a]VIPD: etoposide 100 mg/m$^2$ days 1–3, ifosfamide 1200 mg/m$^2$ days 1–3, cisplatin 33 mg/m$^2$ days 1–3, and dexamethasone 40 mg days 1–4

[b]DeVIC: dexamethasone, 40 mg on days 1–3; etoposide, 67 mg/m$^2$ IV on days 1–3; ifosfamide, 1.0 g/m$^2$ on days 1–3; and carboplatin, 200 mg/m$^2$ IV on day 1

[c]LVP: L-asparaginase 6000 IU/m$^2$ IV on days 1–5, vincristine 1.4 mg/m$^2$ IV on day 1, and prednisone 100 mg given orally on days 1–5. Repeated every 3 weeks

[d]GELOX: gemcitabine 1000 mg/m$^2$ IV on days 1 and 8, oxaliplatin 130 mg/m$^2$ IV on day 1, and L-asparaginase 6000 IU/m$^2$ daily IV days 1–7 every 21 days. For those receiving pegasparaginase, the modified regimen was gemcitabine 1250 mg/m$^2$ IV on day 1, oxaliplatin 85 mg/m$^2$ IV on day 1, and pegaspargase 2500 IU/m$^2$ daily IM on day 1 repeated every 14 days

[e]Modified SMILE: methotrexate 2000 mg/m$^2$ day 1, ifosfamide 1500 mg/m$^2$ days 2–4, etoposide 100 mg/m$^2$ days 2–4, dexamethasone 40 mg days 2–4, and pegaspargase 2000–2500 units/m$^2$ day 8

## *Conventional Treatment Approach for Advanced ENKTCL*

For advanced stage disease (stage III/IV nasal type and stage I–IV extra-nasal type), the primary treatment approach is chemotherapy with an asparaginase-based regimen. Anthracycline-based regimens were used in initial studies, with poor overall response rates. ENKTCL cells express high concentrations of P-glycoprotein, which translates to a multidrug- resistant phenotype [21]. P-glycoprotein is an ATP-dependent efflux pump that exports anticancer agents outside lymphoma cells. This inherent quality of ENKTCL accounts for the disappointing results seen with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and other anthracycline-based regimens [21].

Several studies have demonstrated the efficacy of asparaginase-based chemotherapy regimens for advanced/relapsed/refractory ENKTCL. In a phase II trial using SMILE chemotherapy in 38 patients with advanced nasal-type disease, 20 were newly diagnosed stage IV, 14 were in their first relapse, and 4 patients had refractory disease. Two cycles were planned, and thereafter study participants could

receive further cycles and/or stem cell transplant if recommended by the treating oncologist. Granulocyte colony stimulating factor was included in the protocol based on the phase I study. After two cycles of therapy, the overall response rate was 79%, and the complete remission rate was 45%. A total of 28 patients completed the treatment protocol, and 21 then received a stem cell transplant (4 autologous 17 allogeneic). The 1-year overall survival rate was 55%. Notably, 92% of patients had grade 4 neutropenia, and 61% of patients had infectious complications [22].

In addition to SMILE chemotherapy, other frontline regimens for advanced stage ENKTCL include AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) and P-GEMOX (gemcitabine, pegaspargase, and oxaliplatin). The AspaMetDex regimen was investigated in a phase II prospective study of 19 patients with refractory or relapsed nasal-type ENKTCL. Study participants received three cycles of the 21-day regimen. Objective responses were observed in 73% of patients, and 61% achieved complete remission. The median response duration was 1 year. The most frequent toxicities were cytopenias, abnormal liver function tests, and allergic reactions [23].

The P-GEMOX regimen was investigated in a retrospective study by Wang et al. [20]. Among a cohort of 117 patients, 96 had newly diagnosed disease, and 21 had refractory/relapsed disease. Patients received 2–8 cycles of therapy. The overall response rate was 88.8%, and the 3-year overall survival rate was 72.7%. The most common toxicities were cytopenias, elevated liver function test, and hypertriglyceridemia. Overall, the regimen was tolerated well [16].

## *Role of Stem Cell Transplantation for Treatment of Advanced ENKTCL*

For advanced stage disease, frontline chemotherapy regimen options include SMILE, AspaMetDex, and P-GEMOX. These three regimens have similar overall response rates and toxicity profiles. If patients achieve a complete remission with frontline treatment, stem cell transplantation should be considered. There are no definitive data to guide whether autologous or allogeneic stem cell transplantation should be pursued; decisions must be made individually. If patients only achieve a partial response to chemotherapy, biopsy should be repeated. If negative, stem cell transplantation may be pursued. When patients have a poor response to first-line treatment or if a repeat biopsy is positive, several second-line options may be investigated, including clinical trials. These options for refractory and relapsed disease will be discussed in detail in Sect. II.

## *Prognosis*

The prognosis for all stages of ENKTCL has significantly improved with the use of asparaginase-based chemotherapy. Former scoring systems reflected the prognosis

**Table 10.2** Prognostic index of PINK [21]

| *PINK score risk factors* | *3-year overall survival rate* |
|---|---|
| Age > 60 years | Low – no risk factors – 81% |
| Stage III/IV | Intermediate – 1 risk factor – 62% |
| Distant lymph node involvement | High – 2 or more risk factors – 25% |
| Non-nasal disease | |
| *PINK-E risk factors* | *3-year overall survival rate* |
| All of the above and | Low – zero or 1 risk factor – 81% |
| EBV DNA | Intermediate – 2 risk factors – 55% |
| | High – 3 or more risk factors – 28% |

for patients treated with inferior anthracycline-based regimens. In recent years, a new prognostic index has been developed to more accurately predict patient outcomes.

Kim et al. retrospectively reviewed 527 newly diagnosed patients who received non-anthracycline-based treatments, with the goal of developing a prognostic scoring system. Four factors (age over 60, stage III/IV disease, distant lymph node involvement, and non-nasal disease) correlated with overall and progression-free survival. These factors were used to develop the prognostic index of natural killer lymphoma (PINK) and are shown in Table 10.2. Patients are grouped into one of the three following groups: low-risk disease with no risk factors, intermediate-risk with one risk factor, or high-risk with two or more risk factors. The 3-year overall survival rates for these groups were 81%, 62%, and 25%, respectively [24].

In this study, having a detectable EBV titer was also found to be a prognostic factor for overall survival. The PINK-E model incorporates detectable EBV titer along with the other four risk factors. Patients are divided into three groups: low-risk with one risk factor, intermediate-risk with two risk factors, and high-risk with three or more risk factors. Both models have been validated and are endorsed by the National Comprehensive Cancer Network guidelines. In the future, as therapy options increase and novel agents are introduced, these prognostic models may influence treatment algorithms [24].

## Novel Treatment Options for Advanced Disease

For the management of advanced ENKTCL, asparaginase-based chemotherapy is the recommended frontline therapy. Novel agents are currently being investigated in the relapsed and refractory setting with promising results. These therapies include immunotherapy, Janus-associated kinase (JAK) inhibitors, monoclonal antibodies, pan-class I phosphoinositide 3-kinase (PI3K) inhibitors, and histone deacetylase inhibitors. Given the rarity of ENKTCL and lack of a standard efficacious treatment regimen for those with relapsed or refractory disease, all patients should be evaluated for clinical trials. In this section, novel agents and ongoing clinical trials will be reviewed. A proposed algorithm for management of ENKTCL in both the frontline and relapsed/refractory section will conclude the chapter.

## *Immunotherapy*

Immunotherapy enhances the immune system to fight cancer. Targeted therapies such as checkpoint inhibitors of the programmed death ligand 1 (PDL1) and chimeric antigen receptor T (CART)-cell therapy are two forms of immunotherapy under active investigation for ENKTCL. PDL1 binds to the PD1 receptor on T cells which provides a mechanism for ENKTCL to evade T-cell targeting. ENKTCL expresses PDL1 in 50–80% of tumor cells and infiltrating immune cells, while expression of PD1 is less robust [25, 26]. ENKTCL is characterized by EBV infection, and chronic EBV infection suppresses T-cell cytotoxicity by upregulating PDL1 [27]. Pembrolizumab, a PDL1 inhibitor, which is approved for many solid and hematologic malignancies, is considered an attractive treatment strategy for ENKTCL.

A retrospective study of seven patients who received pembrolizumab after disease progression on asparaginase-based regimen was recently published [28]. Pembrolizumab was given at 2 mg/kg every 3 weeks. All patients were male with a median age of 49 years. The majority of patients (six out of seven) had stage IV disease prior to receiving pembrolizumab. Two of the seven patients had received allogeneic stem cell transplant. Clinical, radiographic, morphologic, and molecular parameters were followed to assess response. All patients had an objective response, and five patients remained in a complete remission after a median follow-up of 6 months. Pembrolizumab was well tolerated. PDL1 expression was found to correlate with treatment responses [28].

Researchers at the Mayo Clinic are currently recruiting patients for a phase II study investigating the efficacy of nivolumab for patients with relapsed or refractory disease. Nivolumab will be given every 14 days for up to eight cycles. Patients who respond will continue therapy every 28 days for up to 24 cycles. The primary outcome measure is the proportion of complete or partial responses assessed according to the revised Lugano Classification Response Criteria (ClinicalTrials.gov Identifier: NCT03075553). Another area of active investigation includes cellular immunotherapy. A phase II trial is underway to evaluate the efficacy of autologous EBV-specific T cells in relapsed/refractory ENKTCL (ClinicalTrials.gov Identifier: NCT01948180).

## *JAK Inhibitors*

As previously detailed in Sect. I, the JAK/STAT pathway is an active oncogenic pathway in ENKTCL. Approximately 35% of all ENKTCL patients have somatic mutations in the JAK3 gene which lead to constitutive activity of the JAK/STAT pathway. Currently, several centers are recruiting patients for a phase II study of ruxolitinib, a JAK inhibitor, in those with relapsed or refractory T- or NK-cell lymphoma. Patients will receive ruxolitinib at a dose of 20 mg twice daily for 28-day cycles. The primary outcome measure is objective response rate (ClinicalTrials.gov Identifier: NCT02974647).

### *Monoclonal Antibodies*

CD38 is a transmembrane protein with expression in several hematologic malignancies. The clinical data of 94 patients with ENKTCL was reviewed by Wang et al., and showed that 95% of patients expressed CD38, but half ($n = 47$) had strong expression of CD38. Further strong expression of CD38 was an independent adverse prognostic feature [29]. In 2016, Hari et al. published a case report using daratumumab, a monoclonal antibody which induces apoptosis of CD38 expressing cells, in a patient with refractory ENKTCL [29]. The case report described a 56-year-old female with relapsed advanced stage ENKTCL who was treated with SMILE chemotherapy. After completing chemotherapy, she went on to receive an allogeneic stem cell transplantation but relapsed within 1 month. Five months following transplant, she was noted to have persistent disease with positive plasma PCR for EBV DNA and received single agent daratumumab at a dose of 16 mg/kg given on a weekly basis. EBV DNA titers increased by a factor of ten during the first 4 weeks of daratumumab treatment, but PCR became undetectable by week 6. She achieved a complete clinical, molecular, and radiographic remission which was sustained at 21-week follow-up. This case report has prompted clinical trials investigating the role of monoclonal antibodies in ENKTCL [27].

### *PI3K Inhibitors*

Latent membrane protein (LMP) 1 is an oncoprotein essential for EBV-driven lymphomas and leads to the activation of signaling pathways which include nuclear factor kB and phosphoinositide 3-kinase (PI3K) [30]. PI3K inhibitors such as copanlisib are currently being studied in relapsed/refractory ENKTCL [31]. Copanlisib is FDA approved for patients with relapsed follicular lymphoma who have failed two prior lines of systemic therapy. It has great promise for a wide range of malignancies from ENKTCL to stage IV cholangiocarcinoma. A phase I/II multicenter study incorporating PI3K inhibitors into the treatment for relapsed/refractory ENKTCL is expected to start recruiting in the near future. Patients will receive copanlisib in combination with gemcitabine. The primary outcome measures are to determine the maximum tolerated dose, dose-limiting toxicities, and the objective response rate.

### *Histone Deacetylase Inhibitors*

In 2017, Zhou et al. investigated chidamide, an oral histone deacetylase inhibitor, in ENKTCL cell lines. Two cell lines were exposed to varying concentrations of chidamide, and proteins involved in multiple signaling pathways were measured using Western blot. Chidamide was found to suppress cell proliferation in a dose- and time-dependent manner. PCR was also employed to measure expression of EBV genes. Chidamide induced expression of lytic phase EBV genes. This novel agent had various antitumor effects via multiple signaling pathways [32].

Histone deacetylase inhibitors are being investigated in multiple phase I and II clinical trials. For instance, a phase II trial investigating panobinostat is underway for patients with relapsed or refractory non-Hodgkin lymphoma. Another promising study is the multicenter phase II trial of panobinostat and bortezomib in patients with relapsed/refractory peripheral T-cell lymphoma or ENKTCL (ClinicalTrials.gov Identifier: NCT00901147).

## *Summary of Treatment Approach*

The management of ENKTCL is evolving with many promising novel agents currently under investigation in clinical trials. Frontline management is dependent on stage and subtype. Figure 10.2a, b provides a summary of the standard treatment

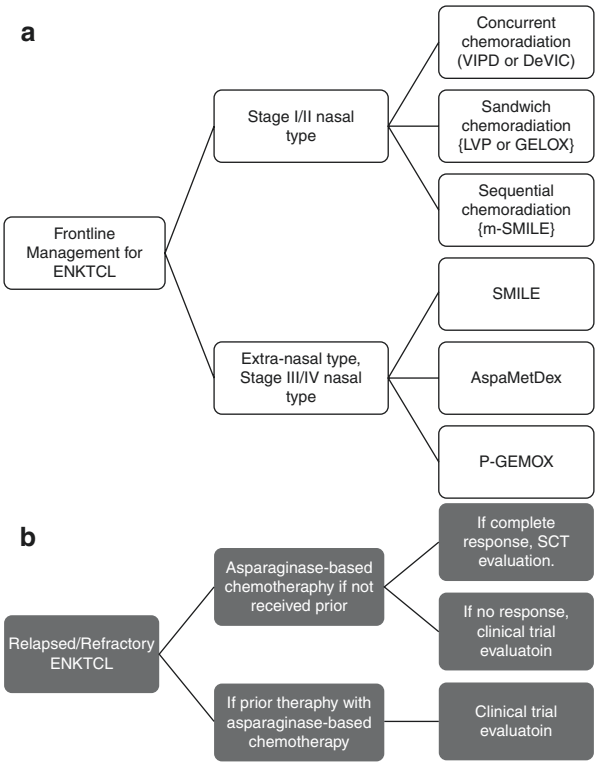


**Fig. 10.2** (**a**) Treatment algorithm for localized, advanced, and extra-nasal ENKTCL. *VIPD* etoposide, ifosfamide, cisplatin, and dexamethasone; *DeVIC* dexamethasone, etoposide, ifosfamide, and carboplatin; *LVP* asparaginase, vincristine, and prednisone; *GELOX* gemcitabine, oxaliplatin, and L-asparaginase; *SMILE* methotrexate, ifosfamide, etoposide, dexamethasone, and pegasparaginase; *AspaMetDex* L-asparaginase, methotrexate, and dexamethasone; *P-GEMOX* pegasparaginase, gemcitabine, and oxaliplatin. (**b**) Treatment algorithm for relapsed/refractory ENKTCL. *CR* complete response, *SCT* stem cell transplant

approach. The role of autologous and allogeneic stem cell transplantation remains controversial. In general, if patients with advanced disease achieve a complete remission with frontline chemotherapy, stem cell transplantation should be considered. In the relapsed and refractory setting, patients should be evaluated for clinical trials. Current therapies being investigated include immunotherapy, JAK inhibitors, immunomodulators, PI3K inhibitors, and histone deacetylase inhibitors.

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