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Extranodal NK/T-cell lymphoma, nasal type (ENKTL-NT): An update on epidemiology, clinical presentation, and natural history in North American and European cases

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Abstract

Extranodal NK/T-cell lymphoma, nasal type (ENKTL-NT) is an aggressive extranodal non-Hodgkin lymphoma most commonly occurring in East Asia and Latin America but with increasing incidence in the U.S. Data on epidemiology, disease presentation, and outcome for European and North American (“Western”) cases are very limited. We review published landmark clinical studies on ENKTL-NT in the West and report in detail recent data, including our institutional experience. We highlight key observations in its epidemiology, natural history, and trends in clinical management. In the U.S., ENKTL-NT is more common among Asian Pacific Islanders

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Conflict of Interest

Bradley M. Haverkos, Zenggang Pan, Alejandro A. Gru, Aharon G. Freud, Rachel Rabinovitch, Meng Xu-Welliver, Brad Otto, Carlos Barrionuevo, Robert A. Baiocchi, and Rosemary Rochford each declare no potential conflicts of interest. Pierluigi Porcu is a section editor for Current Hematologic Malignancy Reports.

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(API) and Hispanics compared to non-Hispanic whites. Published studies indicate less heterogeneity in clinical presentation in Western ENKTL-NT compared to Asian patients. While there is variation in age at diagnosis, presence of antecedent lymphoproliferative disorders, and outcomes among racial/ethnic groups, the universal association of ENKTL-NT with EBV and the poor response of this neoplasm to anthracycline-based therapy are consistent across all geographic areas.

Keywords

extranodal NK/T cell lymphoma; ENKTL; Epstein-Barr virus; United States; Europe; United Kingdom

Introduction

Extranodal NK/T-cell lymphoma (ENKTL), also known as angiocentric T-cell lymphoma, is a rare, extranodal non-Hodgkin lymphoma (NHL) typically affecting the upper aerodigestive tract (UADT), and causing the vast majority of cases of the syndrome previously known as “lethal midline granuloma.” In light of its typical presentation in the nasopharynx, ENKTL has been classified as “nasal type” (ENKTL-NT), a term that has been adopted by the WHO Classification. However, ENKTL-NT frequently extends locoregionally to the paranasal sinuses, orbits, and lymph nodes and in some cases can also develop outside of the nasopharynx.

Nearly all the cases of ENKTL-NT express NK-cell, or less frequently T-cell, markers and one or more cytotoxic molecules, such as granzyme B (GranzB), T-cell-Restricted intracellular antigen-1 (TIA-1), and perforin. In all cases, clonal EBV is found in the majority of tumor cells. The association is so strong that lack of EBV detection should raise doubts about the diagnosis. Most patients present with disease localized to the UADT and have nasal obstruction, epistaxis, and necrotizing lesions of the nose or hard palate. In a subset of patients, ENKTL-NT develop in other extranodal sites, such as the gastrointestinal tract, skin, testis, or lungs. These cases, which display identical morphologic and immunophenotypic features as the UADT cases, including consistent association with EBV, are called *extranasal* or non-UADT ENKTL-NT.

The estimated 5-year overall survival (OS) for ENKTL-NT is between 40 and 50%.¹ Survival is heavily dependent on stage at diagnosis. Long-term follow up suggests a continued risk of relapse up to 10 years from diagnosis.^{2–4} Patients with disseminated ENKTL-NT (regardless of the presenting site) and patients with extranasal, non-UADT ENKTL-NT fare particularly poorly.³

ENKTL-NT has a distinctive ethnic and geographic distribution with higher incidence in East Asia and Latin America, where it can account for upwards of 10% of NHL.^{5–8} In the United States (U.S.), Canada, and Europe, ENKTL-NT is rare, with best estimates indicating that it represents significantly less than 1% of all NHL.^{5–7} ENKTL-NT can mimic other sinonasal and oropharyngeal disorders, such as invasive fungal infections, Wegener’s granulomatosis, and other malignancies, thus resulting in delayed diagnosis and potential

underreporting. The incidence of ENKTL-NT in the U.S. has increased in past few years, with an estimated relative change up to 10% per year according to data from U.S. Surveillance Epidemiology and End Results (SEER).^{9,10} Epidemiology, disease presentation, and outcome data for North American and European patients with ENKTL-NT are extremely limited and conflicting. We review in detail recent studies in the context of previous landmark publications. We highlight discrepancies, limitations, and provide our perspective on the current clinical landscape of ENKTL-NT in the West.

Challenges in the classification of NK/T-cell neoplasms

The classification of the subset of lymphoid malignancies derived from cytotoxic lymphocytes, such as NK-cells, CD8+ (and a subset of CD4+) TCR α/β T-cells, and CD4-, CD8- TCR γ/δ T-cells continues to evolve, reflecting our improved understanding of the biology of these disorders and our appraisal of the significant differences in clinical course and outcome associated with each entity. This has important clinical implications because a diagnosis of lymphoma or leukemia of cytotoxic T-cell or NK-cell derivation in European and North American patients is still associated with a great deal of uncertainty about optimal treatment and anticipated outcome. While many of these entities are clinically aggressive and have poor prognosis, some of them are clinically indolent, have excellent outcomes, and should be managed conservatively. It is therefore important that any potential “sheep in wolf’s clothing”¹¹ is recognized. Since histology and cell lineage are not always discriminating¹², other characteristics, such as presence of EBV or expression of TCR γ/δ , that may help distinguish aggressive from indolent disease entities should be considered. Table 1 provides a summary view of these disorders and outlines the key distinguishing features of the T/NK-cell neoplasms that come under consideration in the differential diagnosis of cytotoxic T/NK-cell neoplasms, including ENKTL-NT.

Since the presence of EBV in cytotoxic T/NK-cell lymphomas is not uniform and may help distinguishing aggressive from indolent subtypes, EBER-ISH should always be included in the diagnostic workup of these malignancies. Among the EBV-positive cytotoxic T/NK-cell neoplasms, ENKTL-NT, is defined in the 2008 World Health Organization (WHO) classification as a “*predominantly extranodal lymphoma characterized by vascular damage and destruction, prominent necrosis, cytotoxic phenotype and association with Epstein-Barr virus (EBV)*.”¹³ Its dual NK/T-cell lineage designation reflects the fact that although most of the cases are derived from NK cells (CD2+, sCD3-, cCD3e+, CD56+, CD16+/-, germline TCR), a subset of cases demonstrate a T-cell phenotype (sCD3+, CD56-, GranB+, with TCR α/β or less frequently TCR γ/δ expression).¹⁴ All cases express one or more cytotoxic markers (GranB, TIA-1, perforin). A number of other aggressive extranodal lymphomas, however, express CD56, cytotoxic markers, and TCR γ/δ .¹² As a result, the distinction between extranasal, non-UADT ENKTL-NT and other lymphoproliferative disorders of NK-cells or cytotoxic T-cells can be quite difficult. In that regard, clinicians and pathologists should also be aware of a group of T-cell lymphomas called *EBV-positive nodal peripheral T-cell lymphoma*.¹⁵ These neoplasms, usually of T-cell α/β lineage, remain included in the PTCL-NOS category in the updated WHO Classification. EBV+ nodal PTCL can express cytotoxic markers, but are generally monomorphic and lack the angioinvasion and necrosis typically observed in ENKTL-NT. Since biological and clinical differences between

ENKTL-NT and EBV+ nodal PTCL may have an impact on treatment and outcomes^{16,17}, defining the cell lineage of ENKTL-NT and assessing EBV status is important. In its 2016 revision, the WHO classification will expand the list of EBV-positive T/NK-cell lymphoproliferative disorders by removing provisional status from a family of neoplasms that typically affects pediatric patients. This group now includes *Systemic EBV+ T-cell lymphoma of childhood* and *Hydroa vacciniforme-like lymphoproliferative disorder* (HVLL).¹⁸ Another existing entity, *Aggressive NK-cell leukemia* (ANKL), remains unchanged.

Among the EBV-negative cytotoxic T/NK-cell lymphoproliferative disorders, the 2016 WHO classification will add two provisional entities: *Chronic lymphoproliferative disorder of NK cells*, generally considered a variant of large granular lymphocyte (LGL) leukemia, and *Indolent T-cell lymphoproliferative disorder of the GI tract*. A third, indolent lymphoproliferative disorder of NK-cells, *NK-cell enteropathy*¹⁹, is not yet included in the 2016 WHO Classification. Although these entities are all characterized by infiltration of extranodal sites with NK-cells or cytotoxic T-cells, mimicking aggressive extranodal T-cell lymphomas and ENKTL-NT, they are clinically indolent and have an excellent prognosis. In the absence of specific molecular or immunologic discriminating features, the absence of EBV should alert pathologists and clinicians that these lesions are not to be included in the family of aggressive T/NK-cell lymphomas, and should therefore be approached as indolent diseases.

Relative frequency of various T/NK-cell lymphomas in the West

Estimating the relative frequency of specific lymphoma entities in geographically different regions of the globe is susceptible to a significant degree of bias, due to inconsistencies in referral patterns, data reporting, and diagnostic criteria. However, when differences are large, comparing relative frequencies can also provide clues to the factors affecting disease development and natural history. The pioneering work conducted by the International Lymphoma Study Group (ILSG) was the first attempt to study the global distribution of NHL subtypes across geographic regions. The ILSG comprised nine institutions in eight countries and collected 1,403 consecutive cases of NHL from 1988 to 1990. This study occurred before the 2008 WHO classification and identified a very small number of “angiocentric nasal NK/T-cell tumors”, mostly from Hong Kong (8%) and Lyon (2%), which likely represented cases of ENKTL-NT.²⁰ For these reasons, it is difficult to generalize about ENKTL-NT from this study. More recently, the International Peripheral T-cell lymphoma project (IPTCLP), a consortium of 22 institutions in North America, Europe, and Asia conducted the largest global comparison study of frequency and clinicopathologic features of mature T-cell and NK-cell lymphomas (defined as PTCL for eligibility purposes), including ENKTL-NT. Among 1,153 cases that met the inclusion criteria for PTCL, 12% (N=136) were classified as ENKTL-NT, of which 68% (N=92) were nasal ENKTL-NT, 26% (N=35) extranasal ENKTL-NT, and ~6% (N=9) were ANKL or unclassifiable. Ethnicity was available for 95% of the cases (129/136). The vast majority of ENKTL-NT patients in the IPTCLP were Asian, overall accounting for 80% of nasal ENKTL-NT and 84% of extranasal ENKTL-NT. White patients accounted for a minority of nasal (9%) and extranasal

(13%) ENKTL-NT cases. The remaining patients registered on the study were Hispanic, Native North American, and African.⁴

Among the cumulative 32 ENKTL-NT cases (5% of PTCL; 32/689) from Europe and North America in the IPTCLP, 66% (21/32) were nasal ENKTL-NT, 25% (8/32) extranasal ENKTL-NT, 3% (1/32) ANKL, and 6% (2/32) unclassifiable. A similar distribution of subtypes was seen among the 104 Asian cases, whereby 68% (71/104) nasal, 26% (27/104) extranasal, 0.01% (1/104) ANKL, and 0.04% (5/104) unclassifiable.⁴ While data on North American, European, and non-Asian ENKTL-NT patients from the IPTCLP are limited, this study represents an unbiased uniform characterization of ENKTL-NT across different geographic areas and ethnicities and demonstrates a similar distribution of subtypes, irrespective of country of origin. Since the main objectives of the IPTCLP were to improve pathologic classification and describe geographic variation in histologic subtypes, clinical data were collected retrospectively, which limits the value of this dataset in describing natural history and outcomes.

In 2006, the IPTCLP launched a new study, the T-cell Project (<https://www.tcellproject.org/>), based on prospective registration of consecutive PTCL patients, including ENKTL-NT, which aims to provide unprecedented paired pathologic and clinical data. As of January 31, 2016, 79 institutions were participating and 1,439 patients with PTCL or NK/T-cell lymphomas had enrolled, with at least 138 ENKTL-NT and 43 other unclassifiable T/NK-cell lymphomas. Only 29% of ENKTL-NT cases are from Asia.²¹ At completion, the T-cell Project will include the largest prospectively collected cohort of Western ENKTL-NT. It will be a valuable prospective dataset to compare the clinical presentation and outcome of ENKTL-NT across racial and ethnic backgrounds. Only patients treated at large academic centers are included, thus there remains a significant degree of selection bias.

Estimating global incidence rates of ENKTL-NT

Since the IPTCLP and the T-cell lymphoma project are not population-based datasets, robust conclusions regarding the incidence of ENKTL-NT cannot be drawn from these studies. Several studies without central pathology review have attempted to compare incidence estimates for Asian and Western T/NK-cell neoplasms. In the U.S., two population based studies compared the incidences of T/NK-cell neoplasms (including ENKTL-NT) in U.S. and Asia. A cross sectional study comparing incidences of hematological malignancies using the Taiwan Cancer Registry and the Surveillance, Epidemiology, and End Results (SEER) in the U.S., identified a higher incidence of T/NK-cell neoplasms in Taiwan vs U.S. (7% vs. 5%) between 2009 and 2010. Wu and colleagues reported a significantly higher incidence of ENKTL-NT in Taiwan, with a standardized rate ratio (SRR), comparable to relative risk, of 2.98 (95% CI 2.08–4.35).²² An additional study using data from the Hong Kong Cancer Registry and U.S. SEER data, compared age-adjusted incidence rates of lymphoid malignancy subtypes in Hong Kong to Asians living in the U.S. and American Whites between 2001 and 2010. Overall, NK/T-cell neoplasms accounted for ~10% (969/9995) of cases in Hong Kong and 6% (6,452/113,669) and 9% (837/9,728) of cases in American Whites and American Asians, respectively. Relative to the rate in Hong Kong (SRR = 1; N = 226) rates of ENKTL-NT were significantly lower in both American Whites

(SRR 0.2; N = 196) and American Asians (SRR 0.5; N = 72).²³ We suspect the higher incidences of ENKTL-NT observed in these U.S. registry studies compared to previous estimates of 1%^{5–7} is due to the inclusion of other subtypes of T/NK-cell neoplasms in addition to ENKTL-NT.

There have been no studies comparing the incidence of ENKTL-NT in Europe vs. Asia, however there have been several population based studies^{24,25}, retrospective analyses^{26–28}, and one prospective clinical trial²⁹ in Europe. In the United Kingdom (U.K.) the Haematological Malignancy Research Network (HMRN) was established in 2004 to provide generalizable data to inform clinical practice and research. It comprises an ongoing population-based cohort of patients newly diagnosed by a single integrated hematopathology laboratory in two adjacent U.K. Cancer Networks. It included 0.001% (9/8355) ENKTL-NT, nasal type patients³⁰ raising the possibility that ENKTL-NT is less frequent in the U.K. compared to the U.S. An Italian study surveyed 10 centers participating in Intergruppo Italiano Linfomi (IIL) and identified 26 cases of non Hispanic whites ENKTL-NT, nasal type between 1997 and 2004.²⁸ While this multi-center Italian study does not provide additional insight into the incidence of ENKTL-NT in Europe, it is one of the few studies with only non-Hispanic whites. In contrast to the scarcity of ENKTL-NT reported throughout Europe, relatively large retrospective ENKTL-NT studies^{26,27} and a prospective clinical trial have been completed in France.²⁹ This suggests that ENKTL-NT may be more infrequent, underreported, or misdiagnosed in certain parts of Europe compared to France. These past and ongoing studies suggest a need to better understand factors responsible for differences in the geodemographic incidence patterns.

Estimates of ENKTL-NT incidence in the West, by ethnic group

Retrospective studies conducted in U.S.^{10,24,31–33}, Europe^{27,28,30}, and Canada³⁴ each with varying limitations have tried to better define the racial patterns of incidence of ENKTL-NT in the West. In the U.S. the National Cancer Data Base (NCDB) is a central database sourced from hospital cancer registry data covering 1500 Commission on Cancer accredited facilities and covers 70% of new cancer diagnoses. There were 596,476 patients diagnosed with NHL from 1998 to 2011 and 3.6% were classified as NK/T-cell lymphomas. The specific incidence of ENKTL-NT was not reported. This U.S. study noted that Hispanics had six-fold higher rates of ENKTL-NT compared to non-Hispanics. Native Americans had similar proportions of ENKTL-NT to Asians.²⁴ A more recent NCDB study presented at the 2016 American Society of Clinical Oncology (ASCO) annual meeting, identified 1,398 (0.2%) ENKTL-NT cases (classified as ICD-0: 9719/3) among 563,833 NHL patients between 1998–2012.³³ Since these studies rely on accurate reporting of ICD (i.e. billing) codes and there is no central pathology review, the diagnostic accuracy of NHL subtypes can be challenged. This may have resulted in the underreporting of ENKTL-NT and over-reporting of other more common subtypes.

Another large study based on SEER data compared the incidence of NK/T-cell neoplasms among U.S. racial and ethnic groups. Thirteen thousand one hundred seven patients with NK/T-cell neoplasms were identified between 2000–2012. Annual incidence of NK-cell neoplasms (ENKTL-NT, N=655 + NK-cell leukemia, N=89) was highest in Asian Pacific

Islanders (APIs) and Hispanics and lowest in blacks and Native Americans.³¹ Inferences about the outcomes of ENKTL-NT from this study have potential to be misleading since “NK-cell leukemia” was included within the category of NK-cell neoplasms in all statistical analyses. Two other U.S. studies used SEER data to show that ENKTL-NT was more common among Hispanics and APIs than non-Hispanic whites. Abouyabis and colleagues studied 3,287 nodal T and T/NK-cell lymphomas between 1992–2005 using SEER data and identified 187 (0.06%) ENKTL-NT resulting in an age adjusted ENKTL-NT incidence rate of 0.036 (95% CI: 0.031–0.042) per 100,000 persons.¹⁰ A second SEER study identified 213 ENKTL-NTs in the California Cancer Registry between 2001 and 2008. ENKTL-NT represented 0.3% (N=65; incidence rate 0.05) of all first primary NHL in non-Hispanic whites, 1.2% (N=91; incidence rate 0.18) in Hispanics, and 1.5% (N=57; incidence rate 0.23) in APIs. As a proportion of all T/NK-cell lymphomas, ENKTL-NTs comprised 1.2% in non-Hispanic whites, 5.1% in Hispanics and 6.8% in APIs.³²

In summary, based on these registry studies^{10,24,32,33}, the best estimates are that in the U.S ENKTL-NT represents ~1–2% of all T/NK-cell lymphomas and ~0.2% of all NHL, with significantly higher incidence among Hispanics and API. These estimates may still be inaccurate for several reasons. First, for registry studies based on billing codes to accurately reflect the incidence of ENKTL-NT, T/NK-cell lymphoma subtypes must be correctly identified and entered into the medical record. In rare and complex hematologic malignancies this assumption is likely invalid. Second, in the IPTCLP, which required centralized pathology review, 12% of all T-cell and NK-cell lymphomas (defined as PTCL) was characterized as ENKTL-NT compared to 0.5% in the most recent SEER study. It's possible that the higher percentage observed in the IPTCLP is an overestimate of ENKTL-NT for several reasons: only large tertiary academic centers were included, it excluded the majority of cutaneous T-cell lymphomas as well as several other T-cell neoplasms (e.g. LGL leukemia), and it included Asian patients. Regardless, the overarching problem is the variation in methodologies across studies, which blurs the exact incidence of ENKTL-NT. Even studies using the same database (e.g. SEER, NCDB) have conflicting results.^{10,24,32,33} It is likely that if diagnoses were revised according to the initial pathology report or centralized pathology review in these registry studies, the incidence of ENKTL-NT would be higher than 0.2% of NHL and 1–2% of T/NK cell lymphomas. To better understand the implications of studies focused on T/NK-cell neoplasms it is critical to understand how the population is defined.

Clinical presentation of ENKTL-NT in different ethnic groups and geographic areas

In the U.S. and Europe, given the low level of suspicion for this neoplasm, diagnosis is often delayed because the biopsy specimen is necrotic or because bacterial and fungal stains are incorrectly interpreted as evidence that the primary process is an invasive bacterial or fungal sinusitis, rather than lymphoma, leading to repeated, but unsuccessful, courses of antimicrobial therapy. This delay in diagnosis and treatment, which may amount to several months, can increase the risk of loco-regional extension, thus compromising survival, and have cosmetically devastating consequences.³ Out of 23 ENKTL-NT patients treated at Ohio

State University (OSU) and 2 at the University of Colorado (CU) we observed a median time of symptoms to diagnosis of 5 months (range 1–36). Twelve patients required more than one diagnostic biopsy leading to considerable delay in diagnosis (up to 36 months). Elevated plasma cell free EBV-DNA (pEBVd) was highly predictive of EBER+ tumors and was very helpful in the workup and diagnosis of patients with suspected ENKTL-NT.³⁵

Just as in Asia, where approximately 70% of patients present with limited stage disease (Ann Arbor Stage I/II) in the nasopharynx, the most frequently reported clinical presentation of ENKTL-NT in the U.S. and Europe is nasal obstruction or bleeding from a mass in the UADT (nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, and larynx).^{26,29,36} Other affected sites reported in the U.S. and Europe include the paranasal area³⁷, skin/soft tissue²⁹, gastrointestinal tract^{38,39}, and testis⁴⁰. Two publications, from the U.S. and France, reported breast involvement^{41,42}, a phenomenon we have observed in the absence of UADT involvement. CNS involvement in ENKTL-NT has not been frequently reported. Two case reports, one from the U.K. and one from the U.S., have described patients with meningeal and CNS disease secondary to CD56–, eCD3+, sCD3–, EBER+ mature T/NK cell lymphomas.⁴³ The largest studies assessing risk of CNS disease in ENKTL-NT are a Swedish registry study⁴⁴ and a retrospective East Asian⁴⁵ study with 0 (0/26) and 6% (12/208) risk of CNS disease, respectively.

In contrast to the relatively uniform UADT presentation in Western ENKTL-NT, Asian and South American cases present with a much more diverse spectrum of clinical manifestations and antecedent disorders. Hemophagocytosis is observed in up to 3% of cases^{36,46–63} and hydroa vacciniforme-like lymphoproliferative disorder (HVLL), an indolent lymphoproliferative disorder of EBV+ NK-cells or γ/δ T-cells can precede ENKTL-NT by several years.⁶⁴ There is no evidence of HVLL preceding ENKTL-NT in U.S. or European ENKTL-NT.

Table 2 displays median age, race, male to female ratio, site of clinical presentation, and stage in published U.S., Canadian, and European studies, as well as unpublished cases from OSU.^{25,28,34,39,65,65} Age at diagnosis in most Asian cohorts is 53 years old², which is similar to the median age of diagnosis in the Western ENKTL-NT studies listed in table 1, as well as a U.S. SEER study³³ (median 53; range 18–90+). Whereas, studies from France, the U.K. (HMRN), and South Korea report median ages at diagnosis between 60 and 63 years.^{3,29,33} In the study directly comparing the Hong Kong Cancer Registry and the U.S. SEER database, the proportion of patients with NK/T-cell neoplasms who were 50 years or older at diagnosis was higher in Hong Kong (70%) and among U.S. Asians (68%) compared to U.S. whites (52%).²³ This differs from the California ENKTL-NT SEER study that showed that non-Hispanic whites were significantly older than Hispanics and API (Non-Hispanic whites 59, Hispanics 52, and APIs 48).³² Due to methodological differences in categorizing T/NK-cell neoplasms in these studies strong conclusions cannot be drawn. However, the significant differences observed in the California study, which focused exclusively on ENKTL-NT, highlight the possibility of an increased genetic susceptibility of Hispanic and API patients, resulting in earlier age of diagnosis.

Virtually all ENKTL-NT studies demonstrate a male predominance. Table 1 shows a ratio of ~2:1 male to female (M:F), which is similar to that reported in an earlier U.S. SEER-based study.¹⁰ This M:F ratio is slightly higher than the 1.8:1 published in a large Korean study by Lee and colleagues,³ but is in line with a large U.S. SEER study by Karkera et al., which reports a M:F ratio 1.9:1.^{2,3,33}

Table 1 shows less frequent extranasal disease in the MD Anderson Cancer Center (MDACC), Italian, and Canadian studies. Whereas, in larger Asian studies, extranasal disease was reported up to 18%.^{2,3} We believe the inconsistency in percent extranasal disease across studies is secondary to differences in inclusion criteria and sample size. The largest U.S. study showed 14% extranasal ENKTL similar to the 15% observed by Lee and colleagues.^{32,33}

With regard to variation among race and ethnicity, Ai et al. showed no difference in stage and site of disease between U.S. (California) Non-Hispanic whites, Hispanics, and API.³² While there may be variation in age of diagnosis among races, ENKTL-NT patients are uniformly male predominant and the differences in clinical presentation (i.e. limited vs. advanced stage and nasal vs. extranasal) observed in some Western ENKTL-NT studies could be explained by sampling bias.

Clinical Outcomes of ENKTL-NT in Europe and North America

The treatment approach to ENKTL-NT has evolved over the years. Early studies showed that anthracycline-based chemotherapy regimens, like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), are largely ineffective in ENKTL-NT, in part due to high levels of expression of P-glycoprotein.⁶⁸ Due to the resistance of ENKTL-NT to chemotherapy, radiation therapy at doses ranging from 45 to 60 Gy was initially adopted as the front-line treatment modality of choice. However, even in stage I ENKTL-NT the rates of progression outside the radiation field in some of the larger studies are unacceptably high.^{66,67} As more effective chemotherapy regimens were integrated in a multimodality approach, concurrent chemo-radiation or sandwich strategies were introduced.

After the initial publication of single agent efficacy with L-asparaginase in relapsed/refractory ENKTL-NT in 2003⁶⁹, Jaccard and colleagues reported an overall response (OR) rate of 87% and a complete response (CR) rate of 47% in 15 Western patients.²⁶ L-asparaginase was incorporated into a variety of combination regimens, dramatically increasing OR rates to ~80%, often with CR rates in the 50–60% range.^{29,70} Based on French studies in relapsed/refractory ENKTL-NT, L-asparaginase appeared equally effective in Western cohorts. Consequently, L-asparaginase-based regimens were introduced in the front-line treatment approach to ENKTL-NT. However, data on upfront use of L-asparaginase in Western ENKTL-NT is sparse, and it remains to be seen whether a strategy of sequential L-asparaginase-based chemotherapy followed by involved field radiation therapy (IFRT) in stage I/II patients is equally effective as CCRT, with regimens such as DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin)⁷¹ and VIPD (etoposide, ifosfamide, cisplatin, dexamethasone)⁷². Recently, the French conducted a prospective study evaluating the efficacy of CCRT using the chemotherapy regimen ESHAP (etoposide,

methyprednisolone, cytarabine, and cisplatin). Thirteen patients with localized ENKTL-NT (Stage I/II) were enrolled between January 2005 and December 2014. This study showed 2-year OS of 72%. In other Western cohorts, as reported in table 1, from MDACC, Italy, and Canada, the majority of patients received anthracycline based therapies with or without radiation. The MSKCC (published) and OSU (unpublished) cohorts include patients who received upfront L-asparaginase.

While the inclusion of L-asparaginase in chemotherapy regimens such as SMILE have dramatically improved response rates in relapsed or advanced stage patients, long term follow up suggests a continued risk of relapse with few long term survivors. Qi et al. reported treating 9 advanced stage (Stage III/IV) ENKTL-NT patients with modified (m) SMILE (4 white, 4 Asian, 1 black). Response rates for these 9 patients were not reported; however, at 1 year follow up, only three patients were alive and only one remained progression-free after initial therapy.⁴⁰ Furthermore, the U.S. NCDB registry study showed no improvements in overall survival when comparing outcomes before and after 2009. Median OS for this entire cohort was 15 months. Improved survival was significantly better in patients who were younger, had early stage disease, nasal only disease, lived in large metropolitan counties, privately insured, received radiation, or underwent stem cell transplant.³³ An alternate U.S. SEER study showed that survival varied significantly by race and ethnicity, with blacks in particular experiencing shorter survival.³¹ As previously discussed, there are multiple limitations to these studies, but results support the need to further investigate factors contributing to variable outcomes in ENKTL-NT between racial and ethnic groups.

The role of autologous and allogeneic hematopoietic stem cell transplant (HSCT) in ENKTL-NT is unclear, with most data deriving from retrospective studies prior to the introduction of non-anthracycline-based front-line treatment strategies.^{73–82} The largest analysis of autologous HSCT for Western patients with ENKTL-NT has been reported by the European Society of Bone Marrow Transplant (EBMT). This study of 28 patients showed 2 year progression free survival (PFS) and OS of 41 and 52%, respectively. Median number of prior therapies was 2 with 57% of patients not in complete remission prior to transplant.⁸³ In a U.S. multi-center retrospective study in 27 ENKTL-NT patients who received autologous and allogeneic HSCT (14 autologous and 13 allogeneic), PFS and OS for the entire group were 50 and 51% with a median follow-up time of 11 years. Overall survival at 3 years for autologous and allogeneic HSCT was 64 and 39%, respectively. There was a trend towards less complete responses prior to transplant in the allogeneic HCT group (46% vs 17%), which suggests a graft versus tumor effect.⁸⁴ These studies demonstrate that HSCT is an effective and useful tool, however knowing who, when, and how to transplant in the asparaginase era remains to be defined.

EBV-DNA monitoring

Based on the detection of EBV-encoded RNA (EBER) in neoplastic NK/T-cells by in situ hybridization (ISH), ENKTL-NT is consistently associated with EBV, irrespective of geographic location or ethnicity.⁸⁵ In many EBV-associated lymphomas, including ENKTL-NT, serum or plasma cell-free EBV-DNA (pEBVd) can be detected and quantified by

quantitative real time polymerase chain reaction (qRT-PCR). Analysis of pEBVd in Asian patients with ENKTL-NT suggests that circulating pEBVd results from shedding of EBV-DNA fragments from latently infected tumor cells.¹⁰¹ Quantitation of pEBVd has been shown in East Asian cohorts to correlate with tumor burden at diagnosis whereby persistent detection after L-asparaginase-based chemotherapy was associated with relapsed or refractory disease.^{73,86–90} Suzuki and others have also suggested that whole blood is a more sensitive tumor biomarker^{1,86,88,91,92}, although serum/plasma and whole blood (PBMC samples) were not drawn in parallel. Kanakry and colleagues, on the other hand, have shown that pEBVd is a more sensitive and specific EBV biomarker across a broad range of EBV-associated diseases.⁹³ Although there were only 3 ENKTL-NT patients studied in this study, all three had elevated cell free pEBVd. Only one patient had a matched PBMC sample, which also contained elevated EBV-DNA.⁹³

Mostly due to limitations of multicenter retrospective data and registry databases, the clinical significance of serially measuring pEBVd and the value of pEBVd as a tumor biomarker in non-Asian ENKTL-NT cases remains less defined. We routinely measure pEBVd in patients with ENKTL-NT at diagnosis, during therapy and at follow up. At OSU 80% of pEBVd-assessable ENKTL-NT patients (17/21) had elevated pEBVd prior to treatment. All 4 individuals without detectable pEBVd at diagnosis had limited stage disease (Stage I). Following initial pEBVd detection at diagnosis, pEBVd rapidly decreased after initiation of therapy and remained undetectable during disease remission in all but one patient who had a transient rise and fall of pEBVd without intervention or relapse. This scenario emphasizes the need to delineate the positive and negative predictive value of pEBVd as a tumor biomarker in ENKTL-NT. Amidst limitations of our clinical assay, in a subset of assessable patients (N=13) we observed a pattern of elevated pEBVd at times of diagnosis, progression, or relapse in 10/13 (77%) patients. (Figure 1) Thus, serial monitoring of pEBVd may be informative as a predictive tumor biomarker also in Western ENKTL-NT.

Proposed Treatment Approach to ENKTL-NT

While there may be differences in genetic susceptibility and clinical presentation between Western and East Asian ENKTL-NT, the poor outcomes associated with anthracycline-based therapies observed in U.S., European, and Canadian populations are comparable to those observed in patients from East Asia. Historically, the evolution of our treatment approach to ENKTL-NT has reflected the initial emphasis on front-line radiation therapy and the use of allogeneic HSCT for eligible patients with chemosensitive progressive disease. With the introduction of more effective, L-asparaginase-based systemic therapies, we have adopted a sequential strategy. At diagnosis we risk stratify patients based on the IPI (international prognostic index) or the KIPi (Korean IPI). With the publication of the PINK-E (prognostic index of natural killer lymphoma with quantitative measurement of EBV-DNA), we have started using this new index.^{3,94,95} Additional negative prognostic markers being explored include beta-2 microglobulin (B2M), soluble interleukin 2 (sIL2) >600 U/mL and C-reactive protein (CRP) >1 mg/dL.^{96,102} In line with NCCN guidelines⁹⁷, we measure pEBVd pre-therapy and during follow up. Consistent with Asian studies, we have observed that measuring pEBVd serially is useful to monitor response and detect relapse. Increasing levels of pEBVd suggest progressive, refractory, or relapsed disease.^{1,86}

Our current front-line approach to ENKTL-NT is largely determined by the IPI/KIPI score, by the extent of disease (Stage I/II vs Stage III/IV), and by pEBVd levels, and is guided by the following considerations: 1) effective systemic therapy is likely an important component of the management strategy for most patients, including those with early stage and 2) the toxicity of CCRT is very significant, even in young and fit patients.^{25,66,67,71,72} These concerns are supported by observations that systemic failure rates after primary radiation therapy are high, even in patients with early stage disease. Therefore, as front line therapy, in patients who are fit and <75 year old, we have adopted the asparaginase-based regimen mSMILE, as published by Qi and colleagues.⁴⁰ For early stage patients who are frail or 75 year old we use less aggressive asparaginase-based regimens or single agent L-asparaginase until clinical improvement and normalization of the pEBVd, followed by IFRT. Three patients (2 OSU, 1 CU) treated with single agent L-asparaginase/IFRT are currently without disease at 6 months to 3+ years after completing therapy. This suggests that single agent L-asparaginase may be adequate in a good risk subset of patients to achieve disease control prior to IFRT and to prevent systemic relapse. In patients eligible for multi-agent chemotherapy we have adopted an approach of stage-adapted mSMILE, followed by IFRT. Patients with Stage I/II, without risk factors (low risk IPI/KIP), receive 2 cycles of mSMILE every 3–4 weeks,⁶⁵ followed by IFRT (45–50 Gy). In our small experience (N=5), this approach to localized disease (Stage I/II) has been encouraging with 100% of the patients achieving a CR (Table 2). Qi and colleagues have experienced similar results with 100% PFS in 11 early stage patients at a median follow up of 2 years.⁴⁰ CCRT regimens such as DeVIC, VIPD, and ESHAP are effective for fit and younger early stage patients. Comparative studies with asparaginase containing regimens (mSMILE, PGemOx⁹⁸) are not available. Radiation alone remains an option for patients with very limited localized disease (Stage I) but the rates of progression outside the field are high.^{66,67}

At our institutions, ENKTL-NT patients with loco-regionally invasive disease and other unfavorable features (B symptoms, elevated LDH, CRP, B2M, extranasal disease) receive 4–6 cycles of mSMILE, followed by IFRT. PGemOx is a consideration in unfit patients. We consider consolidation with autologous HCT for those with advanced stage or high risk patients achieving adequate disease control. We routinely use pegylated asparaginase due to the easier dosing schedule, decreased risk of hypersensitivity, and lower frequency of asparaginase antibodies.⁹⁹ The role of monitoring anti-asparaginase antibodies remains to be defined. In a phase 2 trial in France, PFS and OS were significantly better among patients without antibodies.²⁹ Despite significant improvements in ENKTL-NT outcomes in the asparaginase era, advanced stage patients have poor long term survival.

Conclusions

Western ENKTL-NT is an aggressive lymphoma consistently associated with EBV. Even when accounting for inconsistencies in describing ENKTL-NT vs. other EBV-associated T/NK-cell lymphoproliferative disorders, the incidence of ENKTL-NT in the U.S. appears to be increasing. Despite significant limitations inherent to retrospective and registry studies, there may be differences in age, clinical presentation, and outcome among various racial and ethnic groups. In U.S. populations, ENKTL-NT is more common among API and Hispanics compared to whites. Regardless of variable outcomes among different racial groups, all

patients tend to be resistant to anthracycline based therapy but respond to regimens containing asparaginase. IFRT remains an integral part of therapy for limited stage ENKTL-NT, although high radiation doses (50 Gy) and the need for CCRT may need to be reassessed in the asparaginase era. The timing and role of autologous and allogeneic HSCT are unclear. Plasma levels of EBV DNA provide a measurable tumor marker, with prognostic and predictive implications. While the addition of L-asparaginase has improved complete response rates, advanced stage ENKTL-NT continue to show poor long term survival. Strategies directed at targeting latent EBV in tumor cells are being explored. Novel approaches such as adoptive cellular therapy with EBV-CTLs are a promising and exciting option in need of further investigation.¹⁰⁰

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Impact

Data on epidemiology, disease presentation, and clinical outcomes in mature T-cell and NK-cell (T/NK-cell) neoplasms, including ENKTL-NT, in Europe and North America are very limited. As the classification and diagnostic characterization of the currently recognized T/NK-cell lymphoma disease entities continue to evolve, gaps and inconsistencies in data reporting across different studies are being recognized. Despite these limitations, several studies from the U.S. suggest that the incidence of ENKTL-NT is higher in Asian Pacific Islanders (API) and non-white Hispanics, and that outcomes may be worse in non-whites. However, the universal association of ENKTL-NT with EBV across all ethnic groups suggests a common pathogenesis. Given the overlap between the entities included in the category of T/NK-cell neoplasms, there is a need to further define biological and clinical differences that may affect diagnosis, treatment and outcome.

Figure 1.

Plasma EBV-DNA measurements in ENKTL before, during, and after treatment

Only included when pEBVd was measured during at least 2 time points. Each line in the figure represents one treatment regimen (e.g. CHOP $\times$ 6). Thus, a patient treated with multiple different therapies would have multiple treatment lines. End of therapy (EOT) defined as the first pEBVd measured after completion of treatment (within 2 mos of last therapy). Tx-Treatment; Pts-patients; pEBVd-plasma EBV-DNA measured by quantitative real time PCR

Table 1

Spectrum of T and NK-cell lymphoproliferative disorders and relationship with EBV

Literature Description	2016 WHO Classification	EBV Status	Distinguishing clinical features	Distinguishing pathologic features	Reference
Clinically Aggressive Disorders					
ENKTL	ENKTL nasal type	Positive	Extranodal disease typically with upper aerodigestive tract involvement	Angioinvasive and necrosis; typically sCD3 ⁺ , eCD3 ⁺ , CD56 ⁺ , CD16 ⁺ /–, germ line TCR; subset of T-cell origin (sCD3 ⁺ , CD56 [–]); Clonal EBV NK/T cells	Pongpruttipan, 2012
Aggressive NK-cell Leukemia (ANKL)	ANKL	Positive	Leukemic presentation with blood and bone marrow involvement	sCD3 [–] , eCD3 ⁺ , CD56 ⁺ , germ line TCR; typically CD16 ⁺ ; EBV ⁺ NK cells	Swerdlow, 2008
Angioimmunoblastic T-cell lymphoma (AITL)	AITL	Positive, most	Need to differentiate from inflammatory response due to autoimmune condition or viral infection	Polymorphic; prominent arborizing high endothelial venules with expanded populations of follicular dendritic cells; neoplastic T-cells should express 2 T-follicular helper antigens including CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5; may contain EBV ⁺ B-cell immunoblasts; and predominantly EBV ⁺ B-cells (sometimes clonal)	Swerdlow, 2016
PTCL, follicular variant	Follicular T-cell lymphoma ⁺ and Nodal peripheral T-cell lymphoma with TFH phenotype ⁺	Subset	Need to differentiate from inflammatory response due to autoimmune condition or viral infection	Neoplastic T-cells should express 2 T-follicular helper antigens including CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5; may contain EBV ⁺ B-cell immunoblasts; and predominantly EBV ⁺ B-cells (sometimes clonal)	Swerdlow, 2016
PTCL-NOS	PTCL-NOS	Subset	Typically patients have nodal disease; often in addition to extranodal disease	Monomorphic; Lack angioinvasion and necrosis; Typically sCD3 ⁺ , CD56 [–]	Jung, 2016
EBV⁺ nodal PTCL*	PTCL-NOS	Positive	Typically patients have nodal disease; often in addition to extranodal disease	Monomorphic; lack angioinvasion and necrosis; sCD3 ⁺ and CD56 [–]	Jung, 2016
Enteropathy associated T-cell lymphoma (EATL) Type I	EATL	Negative	Primarily a disease of individuals of northern Europe; associated with celiac disease; need to differentiate from refractory celiac disease	Polymorphic; neoplastic cells of variable size and morphology, with adjacent mucosal findings typical of celiac disease; and typically CD56 [–]	deLeeuw, 2007
EATL Type II	Monomorphic epitheliotropic intestinal T-cell lymphoma	Negative	No association with celiac and primarily in Asians and Hispanics	Monomorphic and typically CD56 ⁺	Swerdlow, 2016
ALCL	ALCL (both ALK ⁺ and ALK [–] variants are now permanent categories)	Negative	Typically patients have nodal disease; often in addition to extranodal disease	Large neoplastic cells; uniformly CD30 ⁺ ; and ALK [–] and ALK ⁺ subtypes	Savage, 2008
Systemic EBV⁺ lymphoproliferative disorder of childhood	Systemic EBV ⁺ T-cell lymphoma of childhood	Positive	Acute EBV infection followed by end organ damage; clinical and pathologic overlap with CAEBV & HLH	Acute EBV infection followed by proliferation of clonal EBV ⁺ T-cells (sCD3 ⁺ , CD56 [–]); and lack cytologic atypia	Cohen, 2009

Literature Description	2016 WHO Classification	EBV Status	Distinguishing clinical features	Distinguishing pathologic features	Reference
Hemophagocytic lymphohistiocytosis (HLH)	Not recognized	Subset	Is <i>not</i> considered neoplastic but may occur secondary to T/NK neoplasm; present with fever and multi-organ disease/failure; elevated ferritin, sIL2, & TG common	~50% are EBV-associated; T-cell proliferation with evidence of hemophagocytosis; EBV+ B or T-cells	Henter, 2007
Clinically Indolent Disorders					
Indolent T-cell lymphoproliferative disorder of the GI tract	Indolent T-cell lymphoproliferative disorder of the GI tract	Negative	Typically presents 1 shallow mucosal ulcers with erythema or multiple small polyps; colonic lesions can be confluent, giving the endoscopic appearance of IBD.	Monomorphic non-destructive clonal small cell infiltrate; no intraepithelial lymphocytes; and typically CD30–	Perry, 2013
NK-cell Enteropathy	Not recognized	Negative	Lesions result in superficial ulceration, edema, and hemorrhage	CD56+, TIA-1+, Granzyme B+, eCD3+, sCD3–	Mansoor, 2011
NK-cell LGL	Chronic LPD of NK-cells ⁺	Negative	Persistent NK-cell lymphocytosis without evidence of alternative NK-cell LPD or inflammatory response due to autoimmune condition or viral infection	sCD3– with germline TCR and either CD56+ or CD16+	Swerdlow, 2016
Chronic Active EBV Infection (CAEBV)	Not recognized	Negative	Recurrent EBV reactivation without evidence of HLH or alternative EBV+ LPD; may be precursor to other T and NK-cell LPDs	EBV-induced clonal expansion of B, T, or NK cells	Jones, 1988
Hydroa-vacciniforme-like lymphoproliferative disorder (HVLL)	HVLL	Positive	Primarily in Central/South America and Asia; necrotic vesiculopapules on sun exposed areas; can progress with systemic dissemination	Polymorphic and typically from clonal T-cells but NK phenotype described	Quintanilla-Martinez, 2000
Hypersensitivity to mosquito bites (HMB)	Not recognized	Subset	Severe local skin reactions and general symptoms such as high fever, liver dysfunction, high IgE levels and regional lymphadenopathy after mosquito bites	NK-cell lymphocytosis is frequently observed in the peripheral blood; Associated with EBV+ LPDs	Ishihara, 1997

⁺ Remains a provisional entity;

^{*} The existence and definition of EBV+ PTCL as a clinically- or pathologically-distinct subset of T-cell neoplasms is controversial and EBV+ PTCL is not a WHO-defined entity; LPD=lymphoproliferative disorder

Table 2
Comparison of clinical characteristics and outcomes in ENKTL cohorts from North America, Europe, and Asia

	Lee et al. (N=262)	MDACC (N=73)	MSKCC (N=43)	Canada (N=34)	Italian (N=26)	France ¹ (N=13)	OSU ² (N=7)
Med Age (range)	79% 59	46 (18–88)	53 (24–81)	53 (23–89)	51 (20–80)	62 (15–86)	48 (32–74)
Race (%)							
White		43 (59)	32 (74)	16 (47)	26 (100)	4 (31)	5 (71)
Hispanic		18 (24)		1 (3)			
Asian	262 (100) ⁶	8 (11)	10 (23)	16 (47)		5 (38)	
Black/Other		4 (6)	1 (3)			4 (38)	2 (29)
Gender (M:F)	13:07	49:24:00	24:19:00	2:01	19:07	9:04	2:05
Type (%)							
Nasal	222 (85)	63 (86)	28 (65)	34 (100)	23 (88)	13 (100)	5 (71)
Extranasal	40 (15)	10 (14)	15 (35)		3 (12)		2 (29)
Stage (%)							
I/II	200 (76)	44 (65)	26 (61)	28 (82)	18 (69)	13 (100)	5 (71)
III/IV	62 (24)	24 (35)	17 (39)	6 (18)	8 (31)		2 (29)
Treatment (%)							
CT	119 (46)	14 (22)	14		9 (34)	13 (100)	5 (71)
Local Tx	18 (7)	8 (13)	2 RT	2	1 (4) ³		
CT+Local Tx	120 (46)	42 (66)	24	32	16 (62) ⁴		2 (29)
Outcomes	5 yr PFS 60% ⁵ 5 yr OS 50%	Med PFS 3yrs Med OS 4.2yrs	2 yr PFS 40% 2 yr OS 60%	2 yr PFS 18% 2 yr OS 39%	Med PFS 14 mos ⁵ Med OS 9 mos	2 yr PFS 72% 2 yr OS 90%	83% CR (5 CR, 1 PD, 1 unk)

Med=Median; MDACC=MD Anderson Cancer Center; MSKCC=Memorial Sloan Kettering Cancer Center; OSU=Ohio State University; unk=unknown; CT=chemotherapy; Local Tx=local treatment with either RT or Sx; Sx=surgery; RT=radiation; PFS=progression free survival; OS=overall survival; yr=year; mos=months;

¹ All treated with concurrent chemoradiotherapy with ESHAP;

²Two treated with asparaginase alone, remaining patients treated with mSMILE;

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³One treated with Sx alone.

⁴Of the 16 treated with CT+ local Tx, 14 treated with RT alone & 2 treated with RT + Sx;

⁵pFS calculated for responders only;

⁶All patients accrued from tertiary hospitals in Korea. Race/ethnicity not reported in manuscript.