NCCN Guidelines® Insights
T-Cell Lymphomas, Version 2.2018
Featured Updates to the NCCN Guidelines

Steven M. Horwitz, MD[1,*]; Stephen M. Ansell, MD, PhD[2,*]; Weiyun Z. Ai, MD, PhD[3]; Jeffrey Barnes, MD[4]; Stefan K. Barta, MD, MRCP, MS[5,*]; Michael Choi, MD[6]; Mark W. Clemens, MD[7]; Ahmet Dogan, MD, PhD[1]; John P. Greer, MD[8]; Ahmad Halwani, MD[9]; Bradley M. Haverkos, MD, MPH, MS[10,*]; Richard T. Hoppe, MD[11,*]; Eric Jacobsen, MD[12]; Deepa Jagadeesh, MD, MPH[13]; Youn H. Kim, MD[11]; Matthew A. Lunning, DO[14,*]; Amitkumar Mehta, MD[15]; Neha Mehta-Shah, MD[16,*]; Yahurio Oki, MD[7]; Elise A. Olsen, MD[17]; Barbara Pro, MD[18]; Saurabh A. Rajguru, MD[19]; Satish Shanbhag, MBBS, MPH[20]; Andrei Shustov, MD[21]; Lubomir Sokol, MD, PhD[22]; Pallawi Torka, MD[23]; Ryan Wilcox, MD, PhD[24]; Basem William, MD[25]; Jasmine Zain, MD[26]; Mary A. Dwyer, MS, CGC[27,*]; and Hema Sundar, PhD[27,*]

Abstract

Natural killer (NK)/T-cell lymphomas are a rare and distinct subtype of non-Hodgkin's lymphomas. NK/T-cell lymphomas are predominantly extranodal and most of these are nasal type, often localized to the upper aerodigestive tract. Because extranodal NK/T-cell lymphomas (ENKL) are rare malignancies, randomized trials comparing different regimens have not been conducted to date and standard therapy has not yet been established for these patients. These NCCN Guidelines Insights discuss the recommendations for the diagnosis and management of patients with ENKL as outlined in the NCCN Guidelines for T-Cell Lymphomas.

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From [1]Memorial Sloan Kettering Cancer Center; [2]Mayo Clinic Cancer Center; [3]UCSF Helen Diller Family Comprehensive Cancer Center; [4]Massachusetts General Hospital Cancer Center; [5]Fox Chase Cancer Center; [6]UC San Diego Moores Cancer Center; [7]The University of Texas MD Anderson Cancer Center; [8]Vanderbilt-Ingram Cancer Center; [9]Huntsman Cancer Institute at the University of Utah; [10]University of Colorado Cancer Center; [11]Stanford Cancer Institute; [12]Dana-Farber/Brigham and Women's Cancer Center; [13]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [14]Fred & Pamela Buffett Cancer Center; [15]University of Alabama at Birmingham Comprehensive Cancer Center; [16]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [17]Duke Cancer Institute; [18]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [19]University of Wisconsin Carbone Cancer Center; [20]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [21]University of Washington/Seattle Cancer Care Alliance; [22]Moffitt Cancer Center; [23]Roswell Park Comprehensive Cancer Center; [24]University of Michigan Comprehensive Cancer Center; [25]The Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute; [26]City of Hope Comprehensive Cancer Center; and [27]National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for T-Cell Lymphomas
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for T-Cell Lymphomas

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:
Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

Individuals Who Provided Content Development and/or Authorship Assistance:

Steven M. Horwitz, MD, Panel Chair, has disclosed that he receives consulting fees from Celgene Corporation; Millenium Pharmaceuticals, Inc./Takeda; Kyowa Hakko Kirin Co., Ltd.; Seattle Genetics, Inc.; Infinity Pharmaceutials/Verastem, Inc.; Mundipharma International Ltd; and ADC Therapeutics. He also receives grant/research support from Celgene Corporation; Millenium Pharmaceuticals, Inc./Takeda; Kyowa Hakko Kirin Co., Ltd.; Seattle Genetics, Inc.; Forty Seven Inc.; Infinity Pharmaceutials/Verastem, Inc.; ADC Therapeutics; and Aileron Therapeutics, Inc.

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Bradley M. Haverkos, MD, MPH, MS, Panel Member, has disclosed that he has no relevant financial relationships.

Richard T. Hoppe, MD, Panel Member, has disclosed that he has no relevant financial relationships.

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Neha Mehta-Shah, MD, Panel Member, has disclosed that she has no relevant financial relationships.

Mary A. Dwyer, MS, CGC, Senior Manager, Guidelines, NCCN, has disclosed that she has no relevant financial relationships.

Hema Sundar, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

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DIAGNOSIS[a]

ESSENTIAL:

- **Hematopathology review of all slides with at least one paraffiin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.**
- **Excisional or incisional biopsy is preferred over core needle biopsy. An FNA biopsy alone is not sufficient for the initial diagnosis of lymphoma.[b] A core needle biopsy is not optimal but can be used under certain circumstances. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core needle biopsy and FNA biopsy in conjunction with appropriate ancillary techniques may be sufficient for diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[c,d]**
  - **IHC panel: For high clinical suspicion of NKTL, first panel should include: cCD3ε, CD56, EBER-ISH[e]**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements[f] or other assessment of clonality[g]**
- **IHC panel:**
  - **B-cell lineage: CD20**
  - **T-cell lineage: CD2, CD7, CD8, CD4, CD5**
  - **Other: CD30, Ki-67**

SUBTYPES

Subtypes included:

- **Extranodal NK/T-cell, nasal type** → **See Workup (NKTL-2)**

Subtypes *not* included:

- **NK-cell leukemias**
- **Precursor NK-cell neoplasm**

[a]It is preferred that treatment occur at centers with expertise in the management of this disease.
[b]Necrosis is very common in diagnostic biopsies and may delay diagnosis significantly. Biopsy should include the edges of lesions to increase the odds of having viable tissue. Useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.
[c]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See B-cell Lymphomas Guidelines).
[d]Typical NK-cell immunophenotype: CD20-, CD2+, cCD3ε+ (surface CD3-), CD4-, CD5-, CD7-/+, CD8-/+, CD43+, CD45RO+, CD56+, T-cell receptor (TCR)αß-, TCRγδ-, EBV-EBER+. TCR and Ig genes are germline (NK lineage). Cytotoxic granule proteins (TIA1, perforin, granzyme B) are usually expressed. Typical T-cell immunophenotype: CD2+ sCD3+ cCD3e+, CD4,5,7,8 variable, CD56+/- EBV-EBER+ TCRαß or γδ+, cytotoxic granule proteins +. TCR genes are clonally rearranged.
[e]Negative result should prompt pathology review for alternative diagnosis.
[f]TCR clonal gene rearrangement results should be interpreted with caution. TCR clonal gene rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of CTCL. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.
[g]Such as FISH, karyotype, genomic analysis.

NKTL-1

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Natural killer (NK)/T-cell lymphomas are a rare and distinct subtype of non-Hodgkin's lymphomas.[1] NK/T-cell lymphomas are predominantly extranodal and most are nasal type, often localized to the upper aerodigestive tract, including the nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, and larynx.[2] However, extranodal NK/T-cell lymphomas (ENKLs) can have an extranasal presentation, with skin, testis, and gastrointestinal tract being the most common sites of extranasal involvement or metastatic disease.[3,4]

Diagnosis

Biopsy specimens should include edges of the lesions to increase the odds of having viable tissue (see NKTL-1; see above). It may also be useful to perform multiple nasopharyngeal biopsies for the evaluation of occult disease even in areas that are not clearly involved on endoscopic examination. Adequate im-

WORKUP

ESSENTIAL:
- History and physical exam with attention to node-bearing areas (including Waldeyer's ring), testicles, and skin
- ENT evaluation of nasopharynx
- Performance status
- B symptoms
- CBC with differential
- LDH
- Comprehensive metabolic panel
- Uric acid
- Bone marrow biopsy + aspirate[h]
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET/CT scan
- Dedicated CT or MRI of the nasal cavity, hard palate, anterior fossa, nasopharynx
- Calculation of Prognostic Index of Natural Killer Lymphoma (PINK)[i]
- Echocardiogram or MUGA scan if treatment includes regimens containing anthracyclines or anthracenedione
- EBV viral load[j] by quantitative PCR
- Concurrent referral to RT for pre-treatment evaluation

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)
- Discussion of fertility and sperm banking
- HIV testing

→ See Induction Therapy (NKTL-3)

[h]BM aspirate - lymphoid aggregates are rare, and are considered involved if EBER-1 positive; hemophagocytosis may be present.
[i]See Prognostic Index of Natural Killer Lymphoma (PINK) (NKTL-A).
[j]EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell, nasal type. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.

munophenotyping is essential to confirm the diagnosis.

Epstein-Barr virus (EBV) infection is always present in ENKL and should be determined using EBV-encoded RNA in situ hybridization (EBER-ISH). A negative EBER-ISH result should prompt hematopathology review for an alternative diagnosis. Clonal T-cell receptor (*TCR*) gene rearrangements have been found in up to a third of cases with ENKL, nasal type (ENKL-NT).[3] Molecular analysis to detect clonal *TCR* gene rearrangements may be useful under certain circumstances. Ki-67 expression has been reported to be prognostic in patients with stage I/II ENKL-NT.[5,6] High Ki-67 expression (≥65%) was associated with a shorter overall survival (OS) and disease-free survival (DFS). In multivariate analysis, Ki-67 expression and primary site of involvement were found to be independent prognostic factors for both OS and DFS.[5]

Workup

Initial workup should include a history and physical examination, laboratory tests, and imaging studies, as outlined on NKTL-2 (see above). Bone marrow involvement is uncommon at diagnosis and occurs in <10% of patients.[7] Morphologically negative biopsies should be evaluated with EBER-ISH and, if positive, should be considered involved.[7–10]

Measurement of EBV DNA viral load using quantitative PCR is useful in the diagnosis and often in the monitoring of disease. EBV DNA viral load correlates well with clinical stage, response to therapy, and poor survival.[11,12] EBV DNA ≥6.1×10^7 copies/mL at presentation has been shown to be associated with an inferior DFS.[11] Pretreatment EBV DNA level in whole blood and plasma has been shown to be a good predictor of response and survival after treatment with asparaginase-based regimens in patients with ENKL-NT.[13–16] In the phase II study from the NK-Cell Tumor Study Group, the overall response rate (ORR) was significantly higher in patients with

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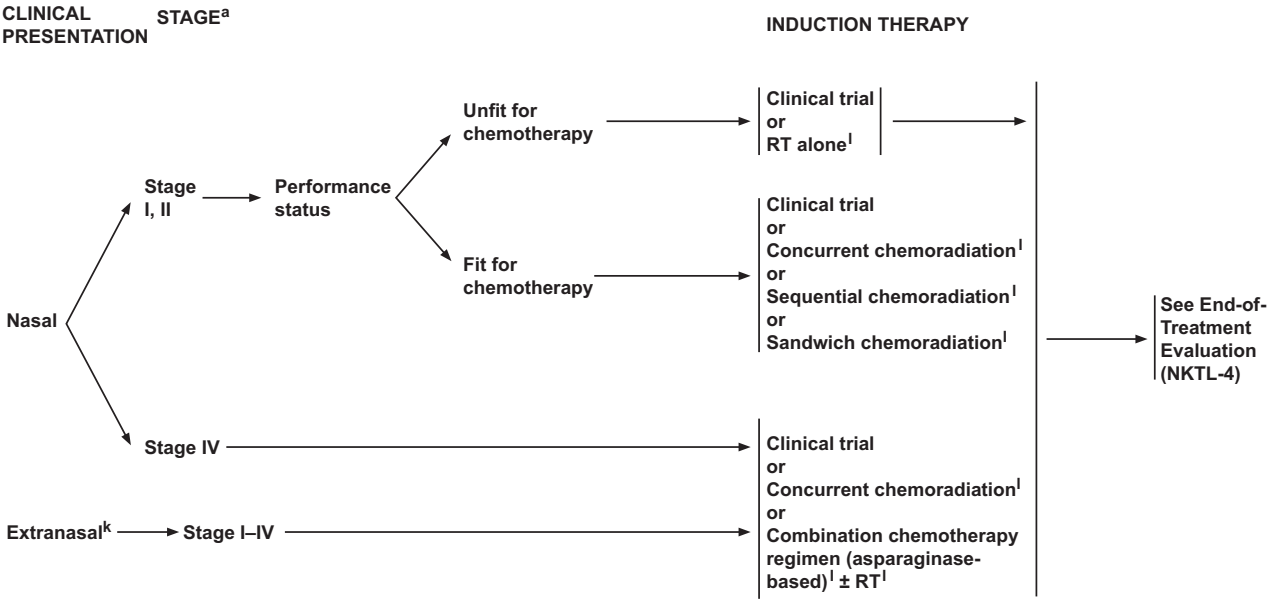


[a]It is preferred that treatment occur at centers with expertise in the management of this disease.
[k]In rare circumstances of stage I_E primary cutaneous NK/T-cell lymphoma, IFRT for solitary skin lesions can be considered.
[l]See Suggested Treatment Regimens (NKTL-B).

NKTL-3

<10^5 copies/mL of EBV DNA in whole blood before initiation of asparaginase-based chemotherapy (90% vs 20%; *P*=.007) and in those with <10^4 copies/mL of EBV DNA in plasma (95% vs 29%; *P*=.002).[15] In addition, the incidence of grade 4 nonhematologic toxicity was significantly higher among patients with ≥10^5 copies/mL of EBV DNA in whole blood (100% vs 29%; *P*=.007) and in those with ≥10^4 copies/mL of EBV DNA in plasma (86% vs 26%; *P*=.002).

A prognostic index of NK lymphoma (PINK) has been proposed for ENKL treated with non–anthracycline-based chemotherapy (NKTL-A; page 129).[17] In a retrospective analysis of 527 patients aged >60 years, stage III or IV disease, distant lymph node involvement, and non–nasal-type disease were identified as predictors of OS and progression-free survival (PFS).[17] Among the 328 patients with data for EBV DNA, detectable EBV DNA measured with quantitative PCR was a significant predictor of OS. Based on these risk factors, PINK stratified patients into 3 risk groups (low-risk [no risk factors]; intermediate-risk [1 risk factor]; and high-risk [≥2 risk factors]) with 3-year OS rates of 81%, 62%, and 25%, respectively. PINK-E (for patients with data for EBV DNA) also stratified patients into 3 risk groups (low-risk [0 or 1 risk factor]; intermediate-risk [2 risk factors]; and high-risk [≥3 risk factors]) with 3-year OS rates of 81%, 55%, and 28%, respectively.

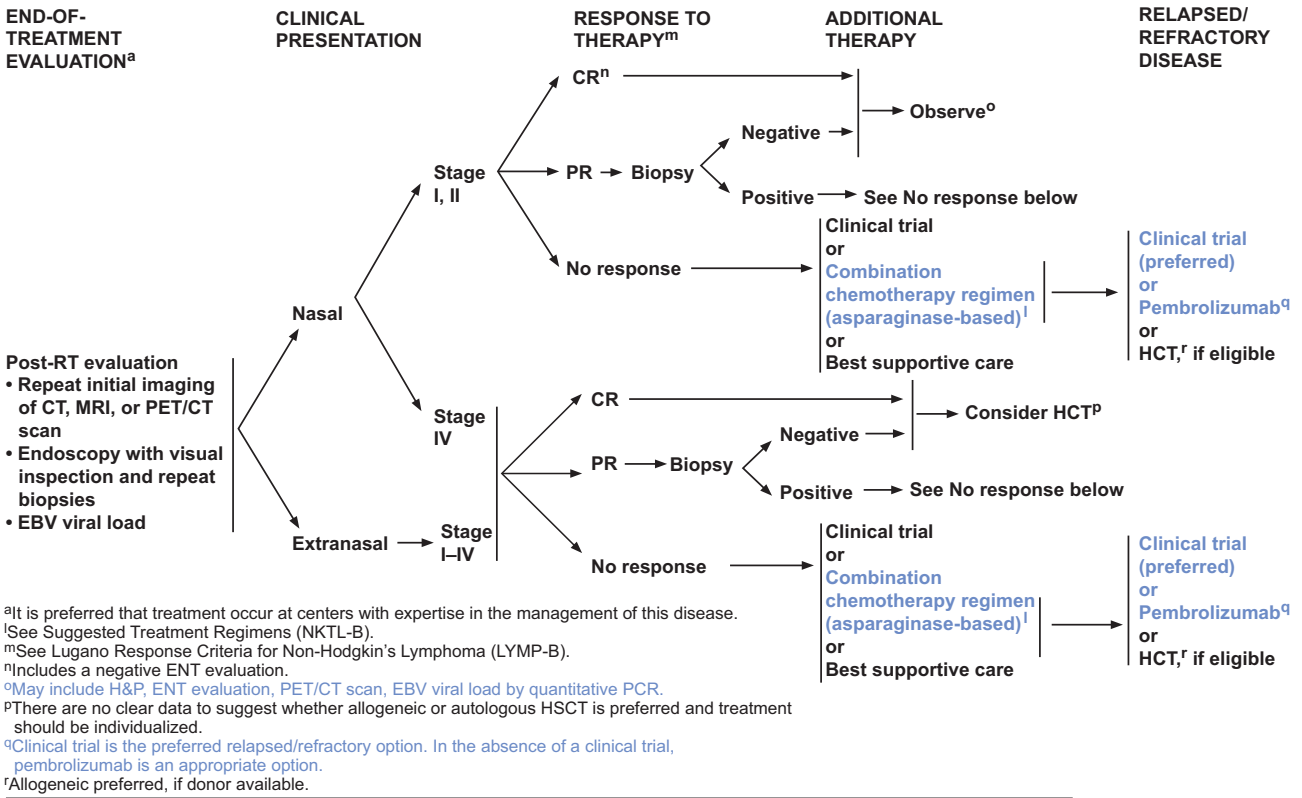
The NCCN Guidelines recommend measurement of EBV-DNA load and calculation prognostic index (PINK or PINK-E) as part of initial workup.

Treatment Options

Radiotherapy With or Without Chemotherapy

Radiotherapy (RT) alone is effective in achieving favorable complete response (CR) rates compared with chemotherapy alone in patients with localized ENKL.[3,18–24]

In an analysis of the International Peripheral T-Cell Lymphoma Project, which retrospectively reviewed the clinical outcomes of 136 patients with



[a]It is preferred that treatment occur at centers with expertise in the management of this disease.
[l]See Suggested Treatment Regimens (NKTL-B).
[m]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (LYMP-B).
[n]Includes a negative ENT evaluation.
[o]May include H&P, ENT evaluation, PET/CT scan, EBV viral load by quantitative PCR.
[p]There are no clear data to suggest whether allogeneic or autologous HSCT is preferred and treatment should be individualized.
[q]Clinical trial is the preferred relapsed/refractory option. In the absence of a clinical trial, pembrolizumab is an appropriate option.
[r]Allogeneic preferred, if donor available.

NKTL-4

ENKL, more patients with ENKL-NT received RT with or without anthracycline-based chemotherapy compared with those with extranasal ENKL (52% vs 24%); the remainder of patients received chemotherapy alone.[3] In the subgroup of patients with early-stage ENKL-NT (n=57), the addition of RT to chemotherapy resulted in a significantly improved 3-year OS rate compared with chemotherapy alone (57% vs 30%; *P*=.045).[3]

In a retrospective review of 105 patients with localized stage I/II ENKL-NT, RT alone resulted in higher CR rates than chemotherapy alone (83% vs 20%), and CR rates improved to 81% among patients who received RT following chemotherapy.[20] The 5-year OS rates were similar among the patient groups that received RT alone (66%; n=31), RT followed by chemotherapy (77%; n=34), and chemotherapy followed by RT (74%; n=37). Notably, in this study, the addition of chemotherapy to RT did not appear to improve OS outcomes.[20]

Early or upfront RT at doses of ≥54 Gy (alone or in combination with chemotherapy) was associated with better survival outcomes in patients with localized ENKL-NT in the upper aerodigestive tract.[21] Among 74 patients who received RT as a component of initial therapy (alone or in combination with chemotherapy), the 5-year OS and DFS rates were 76% and 60%, respectively, for patients treated with RT doses of ≥54 Gy compared with 46% and 33%, respectively, for those treated with RT doses of <54 Gy. Among patients with stage I disease, upfront RT was associated with higher survival rates than early RT following initial chemotherapy (5-year OS rates: 90% vs 49%, respectively; *P*=.012; 5-year DFS rates: 79% vs 40%, respectively; *P*=.021).

RT following chemotherapy also resulted in significantly higher response rates and prolonged survival in patients with advanced-stage disease.[23] In a retrospective analysis of 73 patients with stage III–IV disease, the ORR was significantly higher in patients treated with chemotherapy followed by RT than

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PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA (PINK)[a]

RISK FACTORS

Age >60 y
Stage III or IV disease
Distant lymph-node involvement
Non-nasal type disease

	Number of risk factors
Low	0
Intermediate	1
High	≥2

PROGNOSTIC INDEX OF NATURAL KILLER CELL LYMPHOMA WITH EPSTEIN-BARR VIRUS DNA (PINK-E)[a]

RISK FACTORS

Age >60 y
Stage III or IV disease
Distant lymph-node involvement
Non-nasal type disease
Epstein-Barr virus DNA

	Number of risk factors
Low	0-1
Intermediate	2
High	≥3

[a]Kim SJ, Yoon DH, Jaccard A, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol 2018;17:389-400.

NKTL-A

in those treated with chemotherapy alone (82% vs 29%; *P*<.001). The 2-year OS rates were 58% versus 15%, respectively (*P*<.001), and 2-year PFS rates were 46% versus 8%, respectively (*P*<.001). RT significantly improved the prognosis of patients who experienced CR or partial response (PR) after initial chemotherapy (2-year OS rates: 82% vs 40%, respectively; *P*=.002; 2-year PFS rates: 66% vs 23%, respectively; *P*=.008) but failed to provide a significant survival advantage among those with stable or progressive disease after initial chemotherapy.

Concurrent Chemoradiation

Concurrent chemoradiation (± consolidation chemotherapy) is a feasible and effective treatment for localized ENKL. In the phase I/II study conducted by the Japan Clinical Oncology Group (JCOG0211), high-risk patients with stage I/II nasal disease (n=33; lymph node involvement, B symptoms, and elevated lactate dehydrogenase levels) were treated with concurrent chemoradiation (RT 50 Gy and 3 courses of chemotherapy with dexamethasone/etoposide/ifosfamide/carboplatin [DeVIC]).[25] With a median follow-up of 32 months, 2-year OS was 78% and the CR rate was 77%. Long-term follow-up from this study (median follow-up, 68 months) reported 5-year PFS and OS rates of 67% and 73%, respectively.[26] Late toxicities were manageable with few grade 3 or 4 events, which included only one grade 3 event (irregular menstruation) and one grade 4 event (perforation of nasal skin). The results of a more recent retrospective analysis (358 patients; 257 patients had localized disease) also reported favorable response and survival rates for patients treated with a concurrent RT-DeVIC regimen.[27] After a median follow-up of 5.6 years, 5-year OS and PFS rates were 72% and 61%, respectively. In this analysis, only 4% of patients with localized disease were classified as high risk according to PINK. In multivariate analysis, elevated soluble interleukin-2 receptor was an independent predictive factor for worse OS and PFS among patients treated with RT-DeVIC.

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SUGGESTED TREATMENT REGIMENS[a]

(in alphabetical order)

Combination chemotherapy regimen (asparaginase-based)[b,c]
- AspaMetDex (pegaspargase, methotrexate, and dexamethasone)
- Modified-SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide) x 4–6 cycles for advanced stage
- P-GEMOX (gemcitabine, pegaspargase, and oxaliplatin)

Concurrent chemoradiation therapy (CCRT)
- RT 50 Gy and 3 courses of DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin)
- RT 40–52.8 Gy and cisplatin followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)

Sequential chemoradiation
- For Stage I, II, modified-SMILE x 2–4 cycles followed by RT 45–50.4 Gy

Sandwich chemoradiation[c]
- P-GEMOX x 2 cycles followed by RT 56 Gy followed by P-GEMOX x 2–4 cycles

Radiation therapy alone (unfit for chemotherapy)
- Recommended tumor dose is ≥50 Gy
  - Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.
  - Up-front RT may yield more benefits on survival in patients with stage I disease.

[a]See references for regimens NKTL-B 2 of 2.
[b]See Asparaginase Toxicity Management in the NCCN Guidelines for Acute Lymphoblastic Leukemia.
[c]Pegaspargase-based regimens are preferred. However, there are no data to recommend one particular regimen over another. Treatment should be individualized based on patient's tolerance and comorbidities. P-GEMOX is an option for selected patients who cannot tolerate intense chemotherapy.

NKTL-B 1 OF 2

Another phase II study also reported promising results with concurrent chemoradiation (cisplatin plus RT at 40.0–52.8 Gy) followed by 3 cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) in patients with ENKL-NT (n=30; 21 with stage I/II disease and 9 with stage III/IV disease).[28] The CR rate was 73% after initial chemoradiation and increased to 80% after VIPD. The estimated 3-year PFS and OS rates were 85% and 86%, respectively.[28] The safety and efficacy of concurrent chemoradiation followed by consolidation chemotherapy in patients with localized ENKL-NT has also been confirmed in more recent studies.[29,30]

Asparaginase- or Pegaspargase-Based Chemotherapy or Chemoradiation

ENKL cells are associated with a high expression of P-glycoprotein, leading to multidrug resistance that is likely responsible for the poor response to conventional anthracycline-based chemotherapy.[31] Asparaginase-based or pegaspargase-based regimens have been shown to improve response rates.[32–40]

The SMILE regimen (dexamethasone/methotrexate/ifosfamide/L-asparaginase/etoposide) has been evaluated in patients with newly diagnosed and relapsed/refractory (R/R) ENKL-NT.[32,33] A phase II study from the NK-Cell Tumor Study Group evaluated the safety and efficacy of the SMILE regimen in patients with newly diagnosed stage IV and R/R ENKL-NT (n=38). A total of 28 patients (74%) completed the planned treatment in the phase II study, with an ORR and CR rate of 79% and 45%, respectively.[32] Response rates were not different between previously untreated patients and those with relapsed disease. The 1-year PFS and OS rates were 53% and 55%, respectively.[32] Another phase II study from the Asia Lymphoma Study Group (n=87) also reported favorable outcomes with the SMILE regimen in patients with newly diagnosed and R/R ENKL-NT.[33] The ORR was 81% (CR in 66%), and similar response rates were seen in both groups. At

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SUGGESTED TREATMENT REGIMENS
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Combination Chemotherapy Regimen

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Concurrent Chemoradiation

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Sequential Chemoradiation

Lunning M, Pamer E, Maragulia J, et al. Modified SMILE (mSMILE) is Active in the Treatment of Extranodal Natural Killer/T-Cell Lymphoma: A Single Center US Experience. Clinical Lymphoma, Myeloma and Leukemia 2014;14:S143-S144.

Sandwich Chemoradiation

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Wang L, Wang ZH, Chen XQ, et al. First-line combination of GELOX followed by radiation therapy for patients with stage IE/IIE ENKTL: An updated analysis with long-term follow-up. Oncol Lett 2015;10:1036-1040.

Bi XW, Xia Y, Zhang WW, et al. Radiotherapy and PGEMOX/GELOX regimen improved prognosis in elderly patients with early-stage extranodal NK/T-cell lymphoma. Ann Hematol 2015;94:1525-1533.

Radiation Therapy Alone

Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008;70:166-174.

Relapsed/Refractory Therapy

Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood 2018;129:2437-2442.

NKTL-B
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a median follow-up of 31 months, 4-year DFS was 64% and 5-year OS was 50%.

A modified SMILE regimen (a single dose of pegaspargase is substituted for 7 doses of L-asparaginase per cycle) was also shown to be active for the treatment of ENKL.[34,35] In a retrospective analysis of 43 patients with ENKL-NT treated at a single institution (26 patients with early-stage disease received 2 cycles of chemotherapy followed by 45 Gy of involved-site RT [ISRT]; 17 patients with advanced-stage disease received 3 cycles of chemotherapy alone and ISRT to bulky disease sites), the modified SMILE regimen resulted in a significantly higher CR rate than the accelerated-CHOP regimen (cyclophosphamide/doxorubicin/vincristine/prednisone) (80% vs 30%; P=.015) and the 2-year OS (87% vs 21%) and PFS (56% vs 18%) rates were significantly higher for patients with early-stage versus advanced-stage disease (P<.001) for the total cohort.[35] Among 11 patients with early-stage disease treated with the modified SMILE regimen and 45 Gy of ISRT, the estimated 2-year PFS rate was 83% and all patients were alive with no evidence of disease at the time of publication.

Pegaspargase in combination with gemcitabine and oxaliplatin (P-GEMOX) with or without RT is also an effective treatment option for newly diagnosed and R/R disease.[36,37] In a retrospective analysis of 117 patients with ENKL (96 with newly diagnosed ENKL and 21 with R/R disease), the P-GEMOX regimen resulted in an ORR of 88% and responses were similar for patients with newly diagnosed and R/R ENKL.[36] After a median follow-up of 17 months, 3-year OS and PFS rates were 73% and 58%, respectively. In a subgroup analysis, PFS was significantly better for patients with newly diagnosed ENKL than R/R disease, but there were no differences in OS. The AspaMetDex regimen (L-asparaginase/methotrexate/dexamethasone) was evaluated in a phase II Intergroup study of 19 patients with R/R ENKL.[13] After 3 cycles, patients with localized disease were treated with consolidative RT, if not received previously; those with disseminated disease received high-dose therapy with

peripheral blood stem cell infusion. The ORR and CR rate after 3 cycles of AspaMetDex were 78% and 61%, respectively. Median PFS and OS for both was 1 year; the absence of anti-asparaginase antibodies and the disappearance of serum EBV DNA were significantly associated with a better outcome.[13]

Sandwich chemoradiation (2 cycles of chemotherapy followed by involved-field RT [56 Gy] followed by 2–4 cycles of chemotherapy within 7 days of completion of involved-field RT) with asparaginase- or pegaspargase-based chemotherapy has been shown to be effective for the treatment of patients with newly diagnosed stage I–II ENKL-NT.[38–40] In a phase II study of 27 patients, sandwich chemoradiation with GELOX (L-asparaginase/gemcitabine/oxaliplatin) resulted in an ORR of 96% (CR, 74%). After a median follow-up of 63 months, 5-year OS and PFS rates were 85% and 74%, respectively. Grade 3 or 4 toxicities were infrequent, and no treatment-related deaths were reported.[38] Sandwich chemoradiation with P-GEMOX is also effective for the treatment of patients with newly diagnosed ENKL (n=38), resulting in an ORR of 92% (CR, 87%). At a median follow-up of 15.5 months, the 1-year PFS and OS rates were both 87%.[40]

Hematopoietic Cell Transplant

Autologous hematopoietic cell transplant (HCT) has been evaluated as a consolidation therapy for patients with early- and advanced-stage ENKL responding to primary therapy. In retrospective analyses, disease status at the time of transplant was the most important prognostic factor for OS and relapse-free survival.[41–44] In a retrospective analysis of 62 patients with newly diagnosed ENKL who underwent autologous HCT after primary therapy, those with early-stage disease had significantly better 3-year PFS (64% vs 40%; P=.017) and OS (68% vs 52%; P=.048) than those with advanced disease.[44] In the multivariate analysis, NK/T-cell prognostic index (for limited disease) and pretransplant response (for advanced-stage disease) were independent prognostic factors for survival. In addition, RT was an independent prognostic factor for reduced progression and survival in patients with limited disease, and anthracycline-based chemotherapy was a poor prognostic factor for progression in patients with advanced disease. In a more recent report, pretransplant response status assessed using the Deauville 5-point scale (5PS) and the presence of detectable EBV DNA were identified as independent predictors of OS after autologous HCT.[45]

Allogeneic HCT has also been evaluated in retrospective studies predominantly involving Asian patients.[42,46,47] The use of the SMILE regimen before HCT was the most important positive prognostic indicator for superior OS and event-free survival (P<.01) in patients with stage IV ENKL at first CR or chemotherapy-sensitive R/R disease.[47] In a more recent retrospective analysis from the Center for International Blood and Marrow Transplant Research that evaluated allogeneic HCT in a predominantly Caucasian patient cohort, 3-year PFS and OS rates were 28% and 34%, respectively.[48] Survival rates were similar regardless of the remission status before allogeneic HCT, suggesting that allogeneic HCT may be associated with a survival benefit even in the subset of patients with chemorefractory disease at time of transplant. In a retrospective analysis comparing treatment outcomes for autologous (n=60) versus allogeneic (n=74) HCT in patients with ENKL, the 2-year OS rate was significantly higher with autologous versus allogeneic HCT (69% vs 41%). However, the type of transplant was not a significant prognostic factor in multivariate analysis.[49]

NCCN Recommendations

Participation in a clinical trial is the preferred option for all patients with ENKL with any stage disease. It is recommended that patients with ENKL be treated at centers with expertise in the management of this disease and, when possible, enrolled on clinical trials. Because ENKLs are rare malignancies, randomized trials comparing different regimens have not yet been conducted and standard therapy has not yet been established for these patients. Treatment should be individualized based on patient's tolerance and comorbidities. Retrospective comparative studies have shown that asparaginase- and pegaspargase-based regimens are associated with superior efficacy compared with conventional anthracycline-based regimens for the treatment of stage I–II disease,[50,51] with pegaspargase-based regimens preferred.

Induction Therapy

RT alone is recommended for patients with stage I or II nasal disease who are unfit to undergo chemother-

apy (see NKTL-3; page 127). Patients with stage I or II nasal disease who are fit to receive chemotherapy can be treated with concurrent chemoradiation (RT, 50 Gy, and 3 courses of DeVIC or RT, 40–52.8 Gy, and cisplatin followed by 3 cycles of VIPD) or sequential chemoradiation (modified SMILE followed by RT, 45–50.4 Gy) or sandwich chemoradiation (2 cycles of P-GEMOX followed by RT, 56 Gy, followed by 2–4 cycles of P-GEMOX).

ISRT is recommended as the appropriate field because it limits the volume of RT to the region of involvement only.[52] An ISRT dose of 50 to 55 Gy is recommended when used alone as primary treatment and 45 to 50.4 Gy is recommended when used in combination with chemotherapy. When ISRT is used alone, the clinical target volume (CTV) should encompass the involved region as defined by MRI and CT, with expansions to include any of the sinuses that were partially involved initially, all adjacent paranasal sinuses, and a 0.5- to 1.0-cm expansion into soft tissue.[52] In instances when chemotherapy was given before ISRT and has produced a CR, the CTV should include at least the prechemotherapy gross tumor volume with appropriate margins (0.5–1.0 cm).

Patients with stage IV nasal disease and those with extranasal disease (stage I–IV) can be treated with pegaspargase-based combination chemotherapy (AspaMetDex, modified SMILE, or P-GEMOX regimen) with or without RT, or concurrent chemoradiation (RT, 50 Gy, and 3 courses of DeVIC, or concurrent RT, 40–52.8 Gy, and cisplatin followed by 3 cycles of VIPD). Pegaspargase-based combination chemotherapy alone may be appropriate for selected patients who are not eligible to receive RT. The P-GEMOX regimen is an option for patients who cannot tolerate intense chemotherapy.

Response Assessment and Additional Therapy

End-of-treatment evaluation after induction therapy should include appropriate imaging studies (CT, MRI, PET/CT) based on the type of imaging performed at the initial workup, endoscopy with visual inspection, repeat biopsies, and measurement of EBV DNA (see NKTL-4; page 128). Recent reports from retrospective studies suggest that posttreatment PET/CT using the Deauville 5PS may be a valuable tool for response assessment in patients with newly diagnosed and R/R disease.[53–55] In a retrospective analysis of 102 patients with newly diagnosed ENKL, Deauville 5PS and EBV DNA after completion of initial treatment were independently associated with PFS and OS in the multivariable analysis.[54] Given the primarily extranodal sites of involvement often outside of the chest, abdomen, and pelvis, PET/CT is also preferred for follow-up to better assess these sites.

Patients with stage I or II nasal disease achieving a CR to induction therapy may be observed without further treatment. A CR should also include negative findings on ear, nose, and throat evaluation. Biopsy is recommended for patients with a PR after induction therapy, and those with a negative biopsy may be observed without further treatment. Patients with a positive biopsy should be managed as described in the following section for refractory disease.

Patients with stage IV nasal disease or extranasal disease (stage I–IV) experiencing a CR to induction therapy should be considered for HCT. No clear data suggest whether allogeneic or autologous HCT is preferred, and therefore treatment should be individualized.[49] Biopsy is recommended for patients with a PR after induction therapy, and those with negative biopsy results should be considered for HCT. Patients with positive biopsy results should be managed as described in the following section for refractory disease.

R/R Disease

Second-line therapy with pegaspargase-based combination chemotherapy, as described for induction therapy, may offer benefit for patients with refractory disease (nasal or extranasal, and regardless of disease stage). A clinical trial or best supportive care are also included as options for refractory disease with no response to induction therapy (see NKTL-4; page 128).

A clinical trial is the preferred treatment option for patients with R/R disease after treatment with pegaspargase-based regimens. Pembrolizumab, an anti–programmed death-1 antibody, has been shown to induce high response rates in patients with R/R ENKL after treatment with asparaginase-based regimens.[56] Pembrolizumab is an appropriate option in the absence of a clinical trial. Only limited data exist regarding the role of HCT in this patient population. Allogeneic HCT is preferred if a donor is available.

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Posttest Questions

1. Which of the following are appropriate initial treatment options for early-stage ENKL-NT?
   a. Concurrent chemoradiation with DeVIC
   b. Sandwich chemoradiation with P-GEMOX
   c. Sequential chemoradiation with modified SMILE
   d. All of the above

2. True or False: Detectable EBV DNA measured by quantitative PCR is a significant predictor of PFS and OS in patients with ENKL treated with non–anthracycline-based chemotherapy.

3. True or False: Pembrolizumab is a treatment option for R/R ENKL following treatment with asparaginase-based regimens.