Natural Killer/T-Cell Lymphoma: Saudi Lymphoma Group's Clinical Practice Guidelines for Diagnosis, Management and Follow-up

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Received: 25-03-2019 **Revised:** 06-05-2019 **Accepted:** 24-07-2019 **Published:** 28-08-2019

INTRODUCTION

Natural killer/T-cell lymphoma (NKTCL) is a rare subtype of non-Hodgkin's lymphoma (NHL).[1] According to the Saudi Cancer Registry, in 2015, 829 patients were diagnosed with NHL in Saudi Arabia, of which 24 patients (males = 14; females = 10) (2.9%) were diagnosed with mature T-cell lymphoma.[2]

METHODS

A committee comprising experts in hematology and medical oncology was established under the supervision of the Saudi Lymphoma Group and in collaboration with the Saudi Oncology Society. For collecting evidence, a literature search was carried out with relevant keywords using online database search engines such as PubMed/Medline, Web of Science and Scopus. In addition, expert opinion was considered when necessary.

Access this article online	
Quick Response Code:	Website: www.sjmms.net
	DOI: 10.4103/sjmms.sjmms_104_19

The levels of evidence used in developing this guideline were as follows:

- Evidence level (EL)-1 (highest), evidence from Phase III randomized trials or meta-analyses
- EL-2 (intermediate), evidence from well-designed Phase II trials or Phase III trials with limitations
- EL-3 (low), evidence from retrospective or observational studies/reports and/or expert opinion.

This easy-to-follow grading system is convenient for readers to understand and allows an accurate assessment of the guideline's applicability in individual patients.[3]

1. PATHOLOGIC DIAGNOSIS (EL-1)

1.1. Incisional or excisional biopsy is the preferred method for the initial diagnosis of NKTCL.

1.2. Immunohistochemistry panel should include CD3, cytoplasmic CD3, CD56, CD20, CD2, CD4, CD5,

How to cite this article: Motabi I, Alzahrani M, Dada R, Al-Mansour M, Alhashmi H, Kandil M, *et al*. Natural Killer/T-cell lymphoma: Saudi Lymphoma Group's clinical practice guidelines for diagnosis, management and follow-up. Saudi J Med Med Sci 2019;7:222-5.

CD7, CD8, CD30 and Ki-67.[4-6]

1.3. The diagnosis of NKTCL is confirmed by histopathology features, typical immunophenotyping and documentation of active Epstein–Barr virus (EBV) infection.[4]

1.4. Histopathology features are characterized by tissue necrosis and lymphomatous infiltrate of medium-sized or a mixture of small and large tumor cells.[4]

1.5. Lymphoma cells are typically negative for surface CD3 and CD20, and positive for cytoplasmic CD3 and CD56. Tumor cells are also positive for cytotoxic molecules such as granzyme B, perforin and T-cell intracellular antigen 1.[4,7]

1.6. Documentation of EBV infection is a diagnostic requisite and should be determined by EBV–encoded RNA *in situ* hybridization.[4,8-11] In addition to its diagnostic value, measurement of EBV DNA viral load by quantitative polymerase chain reaction (PCR) has a prognostic value and can also be used for monitoring and response to treatment.[12,13]

1.7. Cases with positive CD56 or cytotoxic molecules in the absence of EBV are classified as peripheral T-cell lymphoma, not otherwise specified (NOS), according to the world health organization (WHO) classification. Similarly, cases positive for EBV but negative for cytotoxic molecules are classified as EBV-positive peripheral T-cell lymphoma, NOS.[4,14]

1.8. Prognostic index: Although many prognostic scoring systems are available, the panel recommends using the PINK-E (prognostic index for NK/T-cell lymphoma-EBV DNA) scoring system (i.e., age, >60; Stages 3 or 4; distant lymph node involvement; non-nasal-type disease; and detectable EBV DNA titer).[15]

2. DIAGNOSIS AND WORKUP (EL-3)

2.1. Evaluations should include detailed history including age, performance status, B symptoms, skin lesions and local ENT symptoms; and physical examination with attention to the oropharyngeal area including Waldeyer's ring, testicles and skin.

2.2. Routine laboratory workup including complete blood count, liver function test, kidney function test, electrolytes, uric acid and lactate dehydrogenase.

2.3. Hepatitis serology

2.4. Bone marrow biopsy is recommended for staging.

2.5. Computed tomography (CT) scan of the chest, abdomen and pelvis.

2.6. CT and magnetic resonance imaging of the neck, nasal cavity and nasopharynx should be performed in all cases.

2.7. Whole-body positron emission tomography scan is recommended, if available.

2.8. Cardiac function should be assessed by echocardiography or multigated acquisition scan.

2.9. Pregnancy test should be done for women of childbearing age.

2.10. Screening test for HIV is required.

2.11. Quantitative EBV DNA by PCR.

2.12. Complete ENT evaluation should be carried out.

3. TREATMENT

There are no randomized controlled studies available to provide treatment guidelines for NKTCL. The best available data are extracted from retrospective reviews and phase II trials. The panel encourages referral of such cases to tertiary care centers.

3.1. Treatment of limited stage (Stages I and II)

Combined modality therapy is the standard and is associated with favorable long-term outcome in limited stage disease. NKTCL is a radiosensitive disease, and radiation therapy alone results in high overall response rate but with an unacceptably high rate of systemic relapse (up to 18%–40%).[16-19] Different combination regimens have been tested in phase II trials with excellent outcome but variable toxicity profiles. The following combined modalities protocols are associated with very good long-term outcome but were not compared in head-to-head studies:

3.1.1. Concurrent chemoradiation therapy (CCRT) and platinum-based chemotherapy:

3.1.1.2. CCRT–DeVIC: Radiotherapy with 50 Gy over 5–6 weeks started simultaneously with dexamethasone, etoposide, ifosfamide and carboplatin (DeVIC). DeVIC is given every 3 weeks for a total of three cycles (EL-2).[20-22]

3.1.1.3. CCRT–VIPD: Radiotherapy with 40–52.8 Gy and weekly cisplatin followed by three cycles of etoposide, ifosfamide, cisplatin and dexamethasone (VIPD) (EL-2).[23-25]

3.1.2. Sandwich chemoradiation:

3.1.2.1. Peg asparaginase, gemcitabine and oxaliplatin (P-GEMOX) or gemcitabine, L-asparaginase and oxaliplatin (GELOX) for two cycles followed by radiotherapy with 56 Gy and P-GEMOX or GELOX for a total of four to six cycles.

3.1.2.2. L-asparaginase, vincristine and dexamethasone (LVD) for two cycles followed by radiotherapy with 56 Gy and

two to four cycles of LVD (EL-2).[26-29]

3.1.3. Sequential chemoradiation:

3.1.3.1. Modified dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide (SMILE) for two to four cycles followed by radiotherapy with 45–50.4 Gy (EL-2).[30]

The above-mentioned combined regimens have a long-term progression-free survival of about 70%–80%. The toxicity profile of the asparaginase-containing sandwich chemoradiation is better compared with the other CCRT regimens. The rates of severe mucositis and bone marrow suppression are higher with CCRT regimens. Additionally, after CCRT–DeVIC, late toxicities occur in about 50% of the patients, including a 5% incidence of secondary malignancy.

3.2. Treatment of advanced stage

Asparaginase-containing combination chemotherapy regimens are the standard treatment for advanced-stage NKTCL. The following regimens are recommended:

3.2.1. SMILE for four to six cycles (EL-3).[31,32]

3.2.2. Dexamethasone, gemcitabine, cisplatin and asparaginase for six cycles (EL-2).[33]

3.2.3. Radiation therapy can be considered for nasal involvement in advanced-stage disease.[34]

3.3. Treatment of relapse and refractory disease:

Asparaginase-containing regimens are effective for the treatment of relapsed NKTCL, even in patients with prior exposure to asparaginase. However, their efficacy in refractory disease is minimal, with only a 25% ORR. In these cases, the following regimens can be used:

3.3.1. L-asparaginase, methotrexate and dexamethasone (AspaMetDex) for 3 cycles (EL-2).[35]

3.3.2. SMILE for four to six cycles (EL-2).[31,32]

3.3.3. P-GEMOX for two cycles (EL-2).[29,36]

3.3.4. In a small study where seven heavily pretreated patients were treated with pembrolizumab, a positive overall response was observed in five patients including three achieving complete remission. All responses were durable after a median follow-up of 6 months (EL-3).[37]

3.3.5. Lenalidomide can be considered in patients who failed more than one line of therapy. There are no studies to support this recommendation but, in a retrospective study of a cohort of patients with relapsed/refractory NKTCL, durable remission was achieved in patients after lenalidomide treatment (EL-3).[38,39]

3.4. Role of hematopoietic stem cell transplantation

3.4.1. The role of hematopoietic stem cell transplantation (HSCT) is not defined in the treatment of NKTCL.

3.4.2. In the early stage disease, combined modality therapy is associated with excellent outcome. Upfront autologous HSCT is not recommended for this indication.

3.4.3. In advanced stage disease, the results of autologous HSCT in retrospective studies are not different from those observed in chemotherapy studies. Therefore, autologous HSCT is not recommended as first-line therapy in advanced stage NKTCL.

3.4.4. Patients with refractory disease have a very poor outcome after autologous HSCT.

3.4.5 SCT might not be necessary for patients who achieved complete remission after SMILE as upfront or salvage protocol, but it should be discussed for selected chemosensitive relapsed or refractory patients (EL-3).

4. FOLLOW-UP

4.1. History and physical examination every 3 months for 1 year, every 6 months for 2 years and then once a year.

4.2. CT examinations are required at 6, 12 and 24 months after the end of treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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