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Review Article

The Diagnosis and Management of Extranodal NK/T-Cell Lymphoma, Nasal-Type and Aggressive NK-Cell Leukemia

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Natural killer (NK) cell lymphomas are rare malignancies. They are classified as extranodal NK/T-cell lymphoma, nasal type, and aggressive NK cell leukemia. NK cell neoplasms are prevalent in Asian and South American populations, but are extremely rare in the West. They can be classified clinically into nasal, non-nasal, and aggressive lymphoma/leukemia subtypes. For nasal NK cell lymphomas, combined chemotherapy and radiotherapy are indicated for stage I/II disease. Chemotherapy is the main treatment for stage III/IV nasal NK cell lymphomas, as well as the non-nasal and aggressive subtypes. Regimens containing drugs not affected by the P-glycoprotein, particularly in combination with L-asparaginase, have resulted in much improvement in treatment outcome for high-risk, refractory or relapsed patients. Autologous or allogeneic hematopoietic stem cell transplantation should be considered for selected patients. Epstein-Barr virus DNA load as a surrogate marker for prognostication, and clinical stratification of patients should be incorporated in clinical management algorithms. 〔*J Clin Exp Hematopathol 51(1) : 21-28, 2011*〕

Keywords: natural killer cell lymphoma, natural killer cell leukemia, chemotherapy, radiotherapy, hematopoietic stem cell transplantation

INTRODUCTION

Natural killer (NK) cells are cytotoxic cells, which are capable of lysing tumor cells, and cells infected by bacteria and virus.[1-3] Morphologically, NK cells appear as large granular lymphocytes with pale cytoplasm and abundant azurophilic granules. The bone marrow is the main site of development of NK cells, which represent a distinct lineage of lymphocytes different from T cells. However, the two lineages are developmentally related, with a bipotential T/NK cell progenitor that can develop into NK cells (without rearrangement of the T cell receptor, TCR, genes), or alternatively into T cells (with rearrangement of the *TCR* genes).[1] Because of a common ontogeny, NK cells express T cell antigens, including CD2, CD7 and CD8. They are negative for surface CD3, but express cytoplasmic CD3 epsilon (ε) chain. NK cells also express "NK-lineage associated" markers, including CD16, CD56 and CD57.[2] Of these antigens, CD56 is generally regarded as an NK cell marker, although it can also be expressed on NK-like T cells, neural and neuroendocrine tissues, and occasionally skeletal muscles.[3]

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HISTOLOGICAL PERSECTIVES OF NK-CELL MALIGNANCIES

Destructive midline facial lesions have traditionally been referred to as lethal midline granuloma.[2] In Caucasian patients, Wegener's granulomatosis, sarcoidosis, carcinomas and conventional sinonasal diffuse large B cell lymphomas are the common causative lesions.[4] However, in Asian and South American patients, these lesions often show atypical lymphoid cells in a polymorphic inflammatory infiltrate of polymorphs, eosinophils and plasma cells, leading to its description as "polymorphic reticulosis".[4] Immunohistochemically, the abnormal lymphoid cells expressed the T lineage antigen CD3. With the recognition of angiocentricity and angiodestruction in these lesions, they were categorized as angiocentric T cell lymphomas in the Revised European American Lymphoma (REAL) classification.[5]

NK CELL LYMPHOMAS

With the availability of anti-CD56 antibodies, most angiocentric T cell lymphomas of the nose and upper aerodigestive tract were found to express CD56.[6] The diagnosis was further improved by the utilization of monoclonal anti-CD3 antibodies that stained only T cells (which expressed surface CD3)

but not NK cells (which only expressed cytoplasmic CD3ε but not surface CD3).[7] Hence, NK cells are surface $CD3^-$, cytoplasmic $CD3\varepsilon^+$, and $CD56^+$, whereas T cells are surface $CD3^+$ and $CD56^+$. Once NK cells became distinguishable from T cells, most nasal angiocentric T cell lymphomas were found to be actually NK cell lymphomas. In the World Health Organization (WHO) classification system, these lymphomas are now classified as extranodal NK/T cell lymphomas, nasal type.[8] The notation of NK/T cell is to cater for the very rare finding of true surface $CD3^+$ and $CD56^+$ cytotoxic T cell lymphomas occurring in the nose, which may be indistinguishable clinically from NK cell lymphomas. However, in clinical practice nearly all NK/T cell lymphomas are actually NK cell lymphomas.

INFECTION OF NK LYMPHOMA CELLS BY EPSTEIN-BARR VIRUS

NK lymphoma cells are almost invariably infected with Epstein Barr virus (EBV).[2,3] Analysis of the EBV terminal repeat region reveals a clonal episomal pattern, suggesting that the virus may be of pathogenetic significance. The consistent presence of EBV has important implications. *In situ* hybridization (ISH) for the EBV encoded early small RNA (EBER) is an accurate localization method for NK lymphoma cells,[9] particularly in sites where EBV is usually absent, such as the liver and bone marrow.[2] In fact, the presence of EBV in the neoplastic cells is a pre-requisite in the WHO classification criteria for NK/ T cell lymphomas.[10]

Chronic active EBV infection and related conditions

NK cell lymphomas may be preceded by uncommon diseases related to EBV infection. Chronic active EBV infection (CAEBV) is a rare condition involving predominantly children and young adults of Japanese, Korean and Chinese decent.[11] Patients present with chronic fever, lymphadenopathy, hepatosplenomegaly and peripheral blood cytopenias, lasting six months or longer. Blood EBV antibody titers and EBV DNA loads are very high. Biopsies of involved tissues show EBV-positive lymphoid infiltrates of either NK cell or T cell lineage. The disease is progressive, culminating in an NK cell leukemia/lymphoma or a T cell lymphoma. Mosquito bite hypersensitivity is a dermatologic condition, with affected individuals developing severe blistering reactions to mosquito or insect bites, often associated with fever and hepatosplenomegaly.[11] These lesions heal spontaneously with scarring, but with time a lesion may continue to deteriorate and develop into a lymphoma of T cell and occasionally NK cell lineage (Fig. 1).

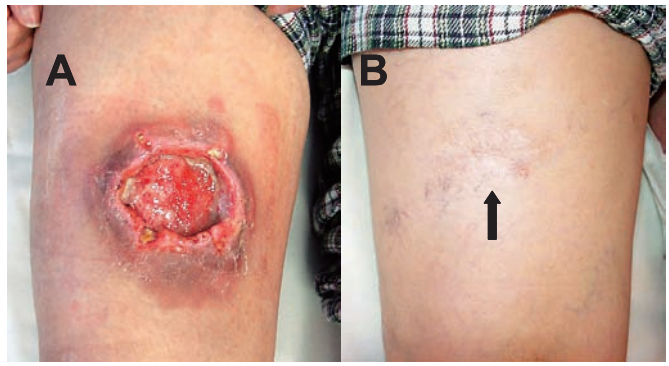

Fig. 1. Mosquito bite hypersensitivity developing into a cutaneous NK cell lymphoma. (***1A***) Cutaneous NK cell lymphoma. (***1B***) Previous scars from mosquito bites on the other leg (*arrow*).

CLINICAL FEATURES OF NK CELL LYMPHOMAS

The WHO classification divides NK cell lymphomas into two subtypes, extranodal NK/T cell lymphoma, nasal type,[8] and aggressive NK cell leukemia.[12] Clinically, NK cell lymphomas can be divided into three categories : nasal, non-nasal, and aggressive lymphoma/leukemia subtypes (Table 1).[2,3]

Nasal NK cell lymphoma

Nasal NK cell lymphomas refer generally to tumors arising in the nose and the upper airway.[13] The male to female ratio is approximately 3 : 1, with disease peaking in the fifth decade of life. NK cell lymphoma is the commonest histologic subtype in nasal lymphomas in Asian patients.[13] Nasal NK cell lymphomas present as destructive mass lesions involving the nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, and larynx. Destruction of the hard palate leads to a characteristic midline perforation, from which the term "lethal midline granuloma" was originally derived (Fig. 2).

Non-nasal NK cell lymphomas

Non-nasal NK cell lymphomas may involve any anatomic site.[14] Male predominance and age of presentation are similar to nasal NK cell lymphomas. Common primary sites include the skin, gastrointestinal tract, salivary glands, spleen and testis (Fig. 3). Interestingly, primary sites of non-nasal NK cell lymphomas are also sites where nasal NK cell lymphomas disseminate to. Hence, it is important for a primary nasal NK cell lymphoma to be excluded before a non-nasal NK cell lymphoma is diagnosed. In practice, patients with NK cell lymphomas involving sites other than the nasal areas should undergo imaging studies and a nasal panendoscopy to exclude an occult nasal primary.[2]

Table 1. Clinicopathological features of different subtypes of natural killer cell neoplasms

Clinical features	Nasal NK cell lymphoma	Non-nasal NK cell lymphoma	Aggressive NK cell lymphoma/leukemia
Sex	Male > Female	Male > Female	Male = Female
Median age	50-60 years	50-60 years	30-40 years
Anatomical sites involved	Nose, para-nasal sinuses, orbits	Skin, gastrointestinal tract, salivary glands, testis, other organs and tissues	Blood, bone marrow, liver, spleen, lymph nodes
Clinical presentation	Nasal bleeding, obstruction, hard palatal perforation	Ulceration and mass lesion	Fever, jaundice, enlargement of liver and/or spleen, lymphadenopathy
Prognosis	Stage I/II : good Stage III/LV : poor	Usually advanced in stage, aggressive, poor outcome	Highly fatal

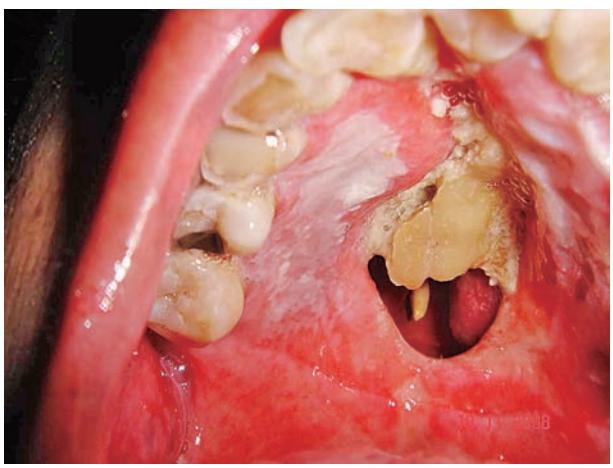

Fig. 2. Palatal perforation due to a nasal NK cell lymphoma

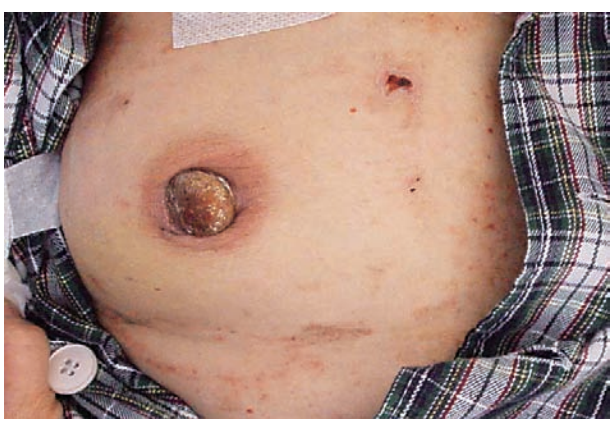

Fig. 3. Non-nasal NK cell lymphoma infiltrating the right nipple

Aggressive NK cell leukemia/lymphoma

Aggressive NK cell leukemia/lymphoma is a catastrophic disorder.[15] Men and women are equally affected, with disease presenting usually at the third decade. Clinical features include high fever, significant weight loss, jaundice, skin infiltration, lymphadenopathy and hepatosplenomegaly. Marrow hemophagocytosis leading to severe anemia and thrombocytopenia may be present. Circulating lymphoma cells vary morphologically from large granular lymphocytes to frank blast. Liver function derangement and disseminated intravascular coagulopathy appear progressively. The clinical course is often lethal, with survival measured just in weeks.

Patterns of dissemination of NK cell lymphomas

Nasal NK cell lymphomas are locally malignant, with distant organ involvement occurring in only about 10% of patients at presentation. Fewer than 10% of cases show marrow infiltration.[16] On the contrary, non-nasal NK cell lymphomas are generally disseminated. With modern imaging techniques, most apparently non-nasal cases can be found to have nasal involvement, implying that they are in fact disseminated nasal NK cell lymphomas. Aggressive NK cell leukemia/lymphoma is disseminated at presentation. It can be differentiated from a rare terminal leukemic form of nasal/non-nasal NK cell lymphoma by the absence of a previous history, a shorter illness, a younger age of presentation, and an extremely aggressive course.

Peripheral blood and marrow involvement in nasal and non-nasal NK cell lymphomas

Peripheral blood cytopenias may be found in about 10-15% of cases of nasal and non-nasal NK cell lymphomas, and

are predominantly due to active hemophagocytosis in the marrow. The hemophagocytic cells represent activated reticuloendothelial cells and on their own do not indicate marrow infiltration. To detect possible lymphomatous infiltration, EBER ISH is a more specific and sensitive test. Staging of nasal and non-nasal NK cell lymphomas should always include EBER ISH in the marrow.[2] Positive results indicated by EBER positive cells in the marrow heralds a grave prognosis.[17]

Initial assessment of NK cell lymphomas

A complete history and physical examination is needed. For biopsy of the involved organ, the specimen should be as sizeable as possible, because zonal necrosis is characteristically found, and a small biopsy may only contain necrotic tissue. The biopsies should be sent fresh unfixed to the pathology laboratory for cryostat sectioning or flow cytometry. This will enable surface CD3 to be detected, which distinguishes between T and NK cell lymphomas. If fresh tumor biopsies are not available, NK and T cell lymphomas can be differentiated by *TCR* gene rearrangement studies, with the *TCR* genes germline in NK cell lymphomas but clonally rearranged in T cell lymphomas.[2,3]

Radiologic imaging is an essential initial evaluation of all clinical subtypes of NK cell lymphomas. Computerized tomographic (CT) scan is better for detection of bony involvement, whereas magnetic resonance imaging (MRI) is superior in defining soft tissue infiltration. Positron emission tomography (PET) is very useful for detection of involvement of other systemic sites. NK cell lymphomas are 18-fluorodeoxyglucose (FDG) avid, with standardized uptake value maximum of about 5-10.[18] Detailed initial imaging is essential for assessment of response. For nasal NK cell lymphoma, radiologic assessment is particularly critical for accurate planning of subsequent radiotherapy.

Quantification of circulating plasma EBV DNA

In EBV-associated lymphoid malignancies, increases in circulating EBV DNA are found, due to viral DNA release from apoptosis of proliferating tumor cells.[19] Serial EBV DNA quantifications by quantitative polymerase chain reaction in NK cell lymphoma have been found to correlate with disease control.[19] EBV DNA quantification can be performed in plasma or whole blood. However, peripheral blood mononuclear cells are not a suitable source, because circulating lymphoma cells are absent.

Staging and prognostication of NK cell lymphomas

As NK cell lymphomas are almost exclusively extranodal, conventional lymphoma staging procedures designed for nodal lymphomas may not always be accurate. To improve patient stratification for treatment, several prognostic models have been applied. The international prognostic index (IPI), taking into account the stage, age, performance status, number of extranodal sites and the lactate dehydrogenase (LDH) level, has been shown to be relevant in NK cell lymphomas.[20] Two other prognostic models based on the IPI concept has also been formulated. When B symptoms, stage, LDH level and regional lymph node involvement are considered, stage I/II nasal NK cell lymphomas can be better stratified into different risk groups.[21] In another prognostic model, non-nasal type, stage, performance status and number of extranodal involvement are found to predict outcome.[22]

MANAGEMENT OF NK CELL MALIGNANCIES

The optimal treatment strategy of NK cell lymphoma has until recently not been well defined. With increased understanding of these malignancies, several important principles have emerged.[23] For nasal NK cell lymphomas, the best treatment results are obtained with a combination of chemotherapy and radiotherapy.[24,25] Chemotherapy is the mainstay of treatment for non-nasal NK cell lymphoma and aggressive NK cell leukemia/lymphoma. Different from conventional lymphomas, anthracyclines have not been shown to be necessary for effective treatment.[20] Frontline high dose chemotherapy and hematopoietic stem cell transplantation (HSCT) is not indicated.[26] Even for cases with relapsed lymphoma, the use of HSCT will still have to be evaluated on an individual basis.[26] Novel treatment approaches are needed to improve the outcome of patients with advanced diseases.

Nasal NK cell lymphoma

For localized stage I/II nasal NK cell lymphoma, radiotherapy used to be the primary treatment. Systemic failure occurred in at least 30% of patients, suggesting that subclinical dissemination of lymphoma had occurred in these apparently early-stage patients.[2] The use of primary chemotherapy was also associated with treatment failure in about 40% of patients, necessitating the use of salvage radiotherapy.[2] Therefore, combined chemotherapy and radiotherapy appears to be the treatment of choice. Chemotherapy and radiotherapy can be given sequentially or concomitantly,[24,25] both methods giving similar treatment results.

Several points are worthy of note. Radiation dosage is typically about 50 Gy, and smaller dosages are associated with inferior outcome when used alone.[2] Whether the dose of radiotherapy can be decreased when concomitant chemotherapy or radio-sensitizer is used remains to be defined.[25] Early use of radiotherapy is important, whether concomitantly or sequentially with chemotherapy.[20] Non-anthracycline based chemotherapy is effective and may be preferable to

anthracycline-containing regimens, particularly in elderly patients. Combined chemotherapy and radiotherapy can be expected to be curative in at least 70-80% of patients with stage I/II nasal NK cell lymphomas.[20,24,25]

Interestingly, very late relapses of early-stage nasal NK cell lymphoma as local or systemic recrudescence have been described to happen after more than ten years to up to thirty years.[27,28] It is unknown if these relapses were derived from the original tumors or represented new lymphomas. Therefore, life-long follow up is recommended even for patients who are in prolonged remission.

Advanced-stage nasal and non-nasal NK cell lymphoma

Chemotherapy is the mainstay of treatment for advanced-stage NK cell lymphomas. Conventional CHOP or CHOP-like regimens give poor outcome, with CR achieved in < 20% of patients.[2] The unsatisfactory result of CHOP may be due to expression of the multi-drug resistance 1 (MDR-1) gene, leading to high levels of P-glycoprotein and therefore active export of many chemotherapeutic drugs including anthracyclines.[3] Hence, non-anthracycline containing regimens may actually be more effective in these patients.

A novel regimen SMILE, comprising dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (Table 2) has been shown in phase I and phase II studies to be promising.[29,30] The regimen is based on the use of drugs not exported by P-glycoprotein together with L-asparaginase, which has been shown to have considerable activities in NK cell lymphomas as a single agent.[31,32] The treatment results of SMILE are remarkable. In patients with relapsed or refractory NK cell lymphoma, SMILE treatment resulted in an overall response (OR) rate of 74%, and complete remission (CR) rate of 35-50%.[29,30] Important side effects include neutropenia and infections, so that aggressive granulocyte colony stimulating factor support is needed. However, the long-term results still remain to be defined.

Relapsed and refractory NK cell lymphomas

The management of patients with relapsed or therapy-refractory NK cell lymphomas is difficult. The therapeutic use of L-asparaginase, either singly or in combination chemotherapy, has led to favorable responses. Different preparations, including E. coli derived, Erwinia-derived, and pegylated forms, appear to have similar treatment results.[31,32] Prospective studies examining L-asparaginase in combination chemotherapy, such as the SMILE regimen, have also shown very good efficacies.[29,30] The main side effects of Lasparaginase include hyperbilirubinemia, liver dysfunction, leucopenia, infections, hyperglycemia, and hypersensitivity reactions. Other drug combinations, including ifosfamide, methotrexate, etoposide, and predonisolone, have also been reported to result in an OR rate of 43.8% and 5-year overall survival (OS) of 24.8%.[33]

Aggressive NK-cell leukemia/lymphoma

Aggressive NK-cell leukemia/lymphoma is a devastating illness, with few treatment successes reported.[2,3] Treatment results of anthracycline-based regimens were dismal, and in one series only three of 13 patients achieved CR, which merely extended the survival for several weeks.[15] Treatment with L-asparaginse-containing regimens followed by allogeneic HSCT had resulted in prolonged survivals in a few cases.[34] This approach will need to be validated.

Hematopoietic stem cell transplantation (HSCT)

Because of unsatisfactory treatment outcome of advanced-staged, relapsed or refractory diseases, the role of autologous and allogeneic HSCT has been explored as consolidation or salvage therapy.[26] However, owing to the relative rarity of NK cell lymphoma, prospective studies of HSCT have not been performed.

Autologous HSCT

In a recent retrospective multi-centre analysis, NK cell lymphoma patients who received autologous HSCT were compared with matched patients who were treated with chemotherapy or radiotherapy only.[35] The disease status before

Table 2. SMILE protocol for advanced stage and relapse natural killer cell malignancies

Drugs	Dosage	Administration	Days
Methotrexate with leucovorin	2 g/m^2	Intravenous	1
Ifosfamide with mesna	1.5 g/m^2	Intravenous	2, 3, 4
Dexamethasone	40 mg	Intravenous or oral	2, 3, 4
Etoposide	100 mg/m^2	Intravenous	2, 3, 4
L-asparaginase	6, 000 U/ m^2	Intravenous	8, 10, 12, 14, 16, 18, 20

Granulocyte colony stimulating factor started on day 6. Cycles to be repeated every 28 days.

HSCT was the most important factor correlating with outcome. Patients with early-stage disease had better outcome than those with advanced or refractory disease. Although patients undergoing HSCT appeared to have a slightly lower relapse rate, a treatment-related-mortality of 8.5% was also observed, so that the OS was not different in the two groups.[35]

Several issues in autologous HSCT remain controversial. Patients with early stage disease limited to the nasal areas are potentially curable with combined chemotherapy and radiotherapy, so that it is doubtful if frontline autologous HSCT may be beneficial.[26] In fact, retrospective analyses appear to show that HSCT in these patients did not confer survival advantage. In patients with advanced-stage or relapsed disease, the results of HSCT remain poor. Whether the application of prognostic models to identify patients who may benefit from early use of HSCT will have to be defined.[35] Finally, conditioning regimens for HSCT in NK cell lymphoma have most often been those used in B-cell lymphomas, including CBV (etoposide, carmustine, and cyclophosphamide) and BEAM (carmustine, etoposide, cytarabine, and melphalan). However, whether these regimens are optimal, or other more effective drugs have to be used, will need to be defined.

Allogeneic HSCT

The potential benefits of allogeneic over autologous HSCT are related a putative graft-versus-lymphoma effect.[2,3] This possibility is attractive, since NK lymphoma cells express EBV viral antigens, which should theoretically be targeted by donor derived cytotoxic T cells reactive to EBV. However, available studies of allogeneic HSCT in NK cell lymphomas are very limited. Problems affecting the interpretation of these studies include differences in donor source (including HLA-matched siblings, unmatched donors, or cord blood), heterogeneity of conditioning regimens (presence or absence of total-body irradiation), and timing of HSCT (at remission, during relapse or refractory disease). In a review of cases reported in the literature, the majority of patients who received allogeneic HSCT had nasal NK cell lymphoma and, at the time of transplantation, 69% had recognizable or refractory diseases. Half of the patients were alive after HSCT, with 25% dying from transplantation-related complications, and the rest from progressive lymphoma.[26] In the largest retrospective series to date, the 2-year OS was 40%.[36] Interestingly, a patient with NK cell lymphoma relapse after allogeneic HSCT achieved a durable remission with discontinuation of immunosuppression, implying the presence of a graft-versus-lymphoma effect.[37] Hence, reduced-intensity-conditioning allogeneic HSCT may also have a role in decreasing treatment-related mortality while preserving the benefits of alloreactivity against lymphoma cells.[38] International collaborative trials are needed to define the optimal use of allogeneic HSCT in NK cell malignancies.

Response evaluation

NK cell lymphomas are predominantly extranodal, so that conventional criteria of response evaluation for nodal lymphoma may not be easily applicable. As NK cell lymphomas are FDG-avid, PET/CT scan is a useful modality. Quantification of circulating EBV DNA is another way of measuring tumor load. The use of PET/CT and EBV DNA quantification in documenting clinical and molecular remission will have to be validated prospectively.

CONCLUSIONS

NK cell malignancies are divided clinically into nasal, non-nasal and aggressive subtypes. There is an almost invariable association with clonal episomal EBV infection. The diagnosis of NK cell lymphoma should be based on morphologic, immunophenotypic, and molecular approaches. Combination chemotherapy and radiotherapy is currently the standard treatment for nasal NK cell lymphoma. For other subtypes of NK cell lymphoma, chemotherapy is the mainstay of treatment. Non P-glycoprotein dependent drugs appear to be efficacious. The optimal timing and indications of autologous and allogeneic HSCT need to be evaluated.

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