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Extranodal natural killer/T-cell lymphoma: current concepts in biology and treatment

HOLBROOK KOHRT and **RANJANA ADVANI**

Division of Oncology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA

Abstract

Natural killer/T-cell (NK/T) lymphomas represent a group of rare tumors of NK and NK-T cells. The World Health Organization classifies NK-cell tumors into three types, extranodal NK/T-cell lymphomas (ENKL, nasal and non-nasal), NK-cell leukemias, and a blastic variant (CD4-positive, CD56-positive hematodermic neoplasms). We focus our review to the current concepts in biology and treatment of ENKL. Though considerable advances have been made in our understanding of NK-cell biology, malignant transformation including the role of Epstein–Barr virus, and prognosis, the rare nature of ENKL and its heterogeneity limit the ability to standardize therapy. Radiotherapy is fundamental to treatment of early-stage disease with a role for chemoradiotherapy among high-risk patients. The clinical course of advanced disease is highly aggressive with frequent chemotherapy resistance and a poor prognosis. Therapeutic approaches to advanced-stage or relapsed and refractory disease, including the appropriate sequence of chemotherapy, combined modality therapy, and stem cell transplantation is not well-established. International and multicenter clinical trials are needed for this rare and aggressive disease.

Keywords

Natural killer; T-cell; lymphoma; diagnosis; treatment

Introduction

Natural killer/T-cell (NK/T) lymphomas represent a group of rare tumors of NK and NK-T cells. NK and NK-T cells are critical components of the innate immune system responsible for anti-viral and anti-tumor immune responses as well as control of autoimmunity. NK cell function is uniquely independent of the T cell receptor (TCR) whereas NK-T cell activity is mediated through a restricted TCR repertoire. Surface markers of both cell types include CD16, CD56, and granzyme with variable expression of classical T cell markers (CD4 and CD8). The World Health Organization (WHO) classifies NK-cell tumors into three types, extranodal NK/T-cell lymphomas (ENKL, nasal and non-nasal), NK-cell leukemias, and a blastic variant (CD4-positive, CD56-positive hematodermic neoplasms) [1,2]. A potential

Correspondence: Ranjana H. Advani, MD, Stanford Cancer Center, 875 Blake Wilbur Drive, Stanford, CA 94305, MC5151, USA. Tel: 650-724-8372. Fax: 650-724-5203. radvani@stanford.edu.

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fourth subtype has recently been reported with an immature NK-cell phenotype, known as precursor NK-cell neoplasm. For the purposes of this review, we will limit our discussion to the current concepts in biology and treatment of extranodal NK/T cell lymphoma. The complex nosology of ENKL includes prior description of this entity as lethal midline granuloma, polymorphic malignant reticulosis, or angiocentric immunoproliferative lesion.

The incidence of ENKL parallels the geographic distribution of Epstein–Barr virus (EBV) infection, which may be directly involved in lymphomagenesis. Histopathologic and molecular advances during the preceding three decades have resulted in improved diagnosis and treatment of NK/T-cell lymphomas. In most patients with advanced disease, the clinical course is highly aggressive with frequent chemotherapy resistance and a poor prognosis. Radiotherapy is fundamental to treatment of early-stage disease with a role for chemoradiotherapy among high-risk patients. Therapeutic approaches to advanced-stage or relapsed and refractory disease, including the appropriate sequence of chemotherapy, combined modality therapy, and stem cell transplantation are not well-established.

Pathobiology

Classic NK-cell tumor histology appears as a polymorphic neoplastic infiltrate with angioinvasion and cytoplasmic azurophilic granules. A diffuse lymphomatous infiltrate is commonly observed with areas of coagulative necrosis, apoptosis and background inflammatory infiltrate including plasma cells, small lymphocytes, histiocytes, and eosinophils. Tumor cells range in size with a mixture of small and large lymphoid cells with irregular nuclei, small nucleoli, and granular or vesicular chromatin. Immunohistochemical (IHC) stains demonstrate expression of T lineage antigens including CD2, CD7, and CD8, whereas NK lineage markers (such as CD56) are consistently expressed. For tumors suspected to be NK lineage it is important for diagnostic testing to be performed on fresh and not formalin-fixed tissue because of nonspecific staining following fixation (polyclonal CD3 is positive in both T and NK cells due to staining of both surface and cytoplasmic CD3 and CD3ε) [3,4]. Evidence of EBV involvement by *in situ* hybridization (ISH) staining for EBV-encoded small nuclear RNA-1 (EBER-1) within transformed cells is critical to diagnosis. Negative ISH for EBER-1 should prompt review of the primary pathology and consideration of an alternative diagnosis. Bone marrow involvement rarely demonstrates lymphoid aggregates, as observed in other lymphoma subtypes, by histology and IHC staining for CD56. However, it is important to evaluate the bone marrow for EBV by ISH for EBER-1. Bone marrow should be considered involved if explicit nuclear staining for EBER-1 is seen within a single non-B cell (EBER-1 positive B cells are observed in chronic EBV infection) [5].

The oncogenesis of ENKL is not well-understood. As other tumors in the nasal cavity and nasopharynx also have an EBV association, the increased incidence of EBV-positive staining within NK-cell lymphomas, particularly nasal-type, has been postulated to be a non-oncogenic marker of EBV within non-malignant cells of the nasal cavity and nasopharynx. However, comparative analysis of the EBV genome in normal cells from the nasal cavity and from ENKL argues for a direct role in pathogenesis. The EBV genome in normal cells from the nasopharynx demonstrates significant strain heterogeneity, while only a single common

EBV strain is found among ENKL tumor cells [6]. In addition, the EBV strain within NK-cell tumors contains a unique, 30-base pair deletion in *LMP1* (latent membrane protein 1) in 96–100% of ENKL cases compared to normal cells which were found to carry wildtype *LMP1* [7,8]. Mutated *LMP1* plays a critical role in cell transformation and immune system evasion because of EBV. Interestingly, cell culture studies have shown retained capacity of EBV to infect NK-cells despite lack of NK-cell surface expression of CD21, the receptor required for EBV adhesion and cell entry [9]. Further support of the role of EBV in the molecular pathogenesis of ENKL includes the observation that circulating EBV DNA titer directly correlates with disease activity and is prognostic with higher titers suggestive of extensive disease, unfavorable response to therapy, and poor survival [10].

Cytogenetic abnormalities are seen in up to 77% of NK-cell neoplasms, particularly in mature NK-cell tumors [11]. Karyotypes observed include pseudodiploidy (57%), hyperdiploidy (30%), and hypodiploidy (13%). Common cytogenetic abnormalities include loss of chromosome 6q, 11q, 13q, and 17p [11]. Deletion of chromosome 6q21–25 and i(6)(p10) are commonly observed by fluorescent in-situ hybridization (FISH) [11]. Molecular analysis of patient samples has also shown inactivation of multiple tumor suppressor genes including *p16NK4A*, *p15NK4B*, *p14ARF*, *TP53, Rb,* as well as mutations in *FAS, B-catenin,* and *KIT* [12]. On an epigenetic level, aberrant methylation of multiple tumor suppressor genes as well as other NK cell-associated genes has been observed. High levels of methylation have been identified in five genes including *p15* (48%), *RARbeta* (56%), *hMLH1* (61%), *p16* (71%), and *p73* (92%) [13]. Methylation patterns are not consistent at the primary tumor compared to metastatic sites, except for *P73* which has similar expression patterns, and has recently been investigated as a marker of disease activity[13].

Clinical features

ENKL presents at a median age of 50 years with a male predominance and a geographic predilection with increased prevalence in Asia, Central and South America [14]. The International Peripheral T-cell Lymphoma Project reviewed 1314 cases and reported a four-fold higher relative frequency of ENKL among lymphomas in Asian countries compared to Western countries (22% *vs.* 5%) [15]. At diagnosis, 80% of cases involve the upper aerodigestive tract (UAT), inclusive anatomically of the nasal cavity, nasopharynx, oral cavity, oropharynx, and hypopharynx [16]. In the nasal type, 70% of patients present with localized disease resulting in symptoms at presentation including purulent rhinorrhea, epistaxis, and local swelling because of anatomical obstruction [16]. Extension into the hard palate leads to destruction with a characteristic mid-line perforation. Clinically, ENKL is the most common lymphoma subtype which presents within the nasal cavity, occurring along the midline at sites including the nasopharynx, paranasal sinus, tonsils, hypopharynx, larynx, and nasal cavity itself. However, in 10% ENKL may present in “extranasal” sites with a predilection for the gastrointestinal tract, skin, salivary glands, adrenals, spleen, and testis. Bone marrow and central nervous system involvement at presentation are rare, <3% and 7%, respectively [17]. The majority of patients with extranasal ENKL present with B symptoms, advanced stage, and evidence of hemophagocytosis with resultant cytopenias [15].

The diagnostic evaluation is similar to other lymphomas; however given the unique anatomic sites of involvement, dedicated imaging studies of the nasal cavity, hard palate, and anterior fossa are required. Panendoscopy including the oropharynx and stomach should be considered in all cases given the propensity for UAT involvement. The utility of fluorine-18 fluorodeoxyglucose positron emission tomography (PET) has demonstrated high sensitivity, greater than 95%, for extracutaneous disease, with the exception of cutaneous or bone marrow involvement [18,19]. Given this sensitivity, PET imaging may replace the role of panendoscopy. An MRI is also recommended as it provides a clearer distinction between soft tissue and bone involvement compared to PET-CT, and is useful in radiotherapy planning. Independent assessment of marrow involvement and a thorough physical exam remain necessary for adequate staging.

Prognostic factors

Accurate assessment of patient prognosis is important for identification of patients at low risk for recurrence with early-stage disease and selection of patients at high risk to receive high-dose, intensive therapies. The 5-year overall survival (OS) in early-stage disease is over two-fold superior to advanced-stage at diagnosis, 54% *versus* 20% [20]. Even within early-stage disease, patients with stage I disease have a long-term OS double that of stage II disease [21]. However, as ENKL often presents with extranodal disease, standard lymphoma staging, such as Ann Arbor stage, is limited in its applicability. Several earlier series suggest that anatomical location is prognostic including comparison of ENKL within the UAT *versus* non-UAT [22]. The UAT tumors have a higher rate of complete remission (CR) with initial therapy (60% *versus* 32%), and a 5-year OS approximately two-fold greater compared to non-UAT tumors (41–54% *versus* 20–22%) [20,23].

Multiple efforts have attempted to select new prognostic markers. In multivariate analyses across studies, independent predictors of OS include age over 60, lactate dehydrogenase (LDH)above the upper limit of normal, elevated C-reactive protein (CRP), eastern cooperative oncology group (ECOG) performance status greater than 2, presence of B symptoms, or histological evidence of high Ki-67 staining, hemophagocytosis, and local invasion (such as bone or skin invasion; Table I) [22,25,26]. Local tumor invasiveness increases the relative risk of progression and death by 7.3- and 2.8-fold, respectively [27].

There is ongoing debate regarding the applicability of the International Prognostic Index (IPI), a standard prognostic index in diffuse large B-cell lymphoma, in ENKL. Comparison of IPI between studies is limited by small sample size and heterogeneity of therapy. Series which support IPI as prognostic are weighted toward early-stage disease, and report a 20-year OS of 57% among patients with IPI ≤1 compared to 27.6% in patients with an IPI of 2 or more [28,29]. Because of the inability of the standard IPI to distinguish between low- and intermediate-risk patients a new prognostic model (NK/T cell PI) has been proposed [24,30,31]. This model was based on a retrospective review of 262 cases with low- and high-risk disease by IPI, and included four variables (presence of B symptoms, Ann Arbor stage III or IV, elevated LDH >normal, and presence of regional lymphadenopathy (N1 through N3, not M1)). Four risk groups were identified. The 5-year OS for patients with low-risk (0 factors) and low-intermediate risk (1 factor) were 80.9% and 64.2%, respectively. Patients

with intermediate-high-risk (2 factors) and high-risk (3 or 4 factors) had a 5-year OS of 34.4% and 6.6%, respectively. Disappointingly, both the NK/T-cell PI and IPI were only prognostic for nasal type, with neither index predictive among patients with extranasal disease in the International Peripheral T-cell Lymphoma Project [15].

The inadequacies of clinical and laboratory-based prognostic models have led to the exploration of biological-based factors. Given prior implication of EBV in ENKL oncogenesis, Au *et al*. [10] evaluated whether EBV activity correlated with disease course and outcomes. Plasma EBV DNA levels by quantitative PCR correlated with stage of disease and response to therapy. In multivariate analysis, EBV DNA levels >6.1 $\times 10^7$copies/mL were significantly associated with inferior disease-free survival (DFS). EBV DNA titer may also be evaluated within whole blood, where it has similarly been shown to correlate with stage at diagnosis, prognosis, and response to therapy [10,32]. However, whole blood EBV PCR may lead to possible inaccuracy due to detection of EBV-infected memory B cells. The effect of EBV status on prognosis may be modified by coexistent genetic mutations. Assessment of EBV by RNA ISH for EBERs and concurrent cytogenetic abnormalities has identified co-expression of EBER with a p53 mutation as highly predictive of treatment failure [33].

Expression of an emerging prognostic marker, CD94, a subtype of NK-cell antigen receptor correlates with increased NK-cell maturation as well as a better prognosis. In one series, eight of ten CD94-positive patients were alive beyond 1 year, compared to two of nine CD94-negative patients (60 *versus* 10-month median survival)[34]. S-phase kinase-associated protein 2 (Skp2, a subunit of the ubiquitin protein ligase complex) is found at increased levels in the majority of NK-cell lymphomas. Patients with Skp2 expression and loss of p27 have worse OS [35]. Other emerging prognostic markers include absence of granzyme B inhibitor PI9, expression of cutaneous lymphocyte antigen, missense mutations of *TP53*, and high serum levels of nm23-H1 protein [9]. At present, clinical and laboratory assessments remain the standards for risk assessment in NK lymphomas. EBV disease activity is a promising additional source of prognostic information. Newer molecular markers require additional study but offer hope for improved risk stratification and guiding treatment selection in the future.

Treatment

There remains a lack of consensus on treatment of ENKL and no therapy is considered standard. Most data are limited by small, non-randomized studies, inconsistent diagnostic criteria, and heterogeneous patient populations, with older series containing non-ENKL cases. Finally, as case series are reported from several countries, direct comparison of results is further limited by varying technology in tissue staining and processing, standards of medical care, and patient genetic makeup. Recognizing these limitations, for the purposes of this review, we have discussed treatment organized by stage and modality, and have suggested an algorithm for approach to management (Figure 1).

Early-stage

Experience with radiotherapy alone—Table II summarizes the experience with radiation therapy, chemotherapy, and combined modality therapy in the management of early-stage ENKL, both nasal and extranasal (non-nasal). There are no randomized trials comparing radiation therapy to chemotherapy. Prior to current diagnostic classification of NK-cell tumors, radiation was recognized as critical to inducing durable complete remissions in lethal midline granuloma and has remained the cornerstone of therapy for early-stage ENKL [42].

The largest series with radiation as a single modality treatment included 143 patients accrued over 20 years in which the majority had nasal-type, early-stage disease [36]. Of 143 patients, 104 received upfront radiation with a median dose of 50.4 Gy (range of 20–70 Gy). Sixty-nine percent of patients treated with radiotherapy alone achieved CR, while only 8% achieved a CR following chemotherapy administered prior to radiotherapy. Other smaller series have reported similar outcomes with CR rates between 52 and 100% [25,26,31,38–40]. Many of these support a potential OS benefit to radiation therapy alone compared to no treatment or chemotherapy alone with an absolute improvement in 5-year OS of up to 26% [25,26,31,37–40].

The benefit of radiation in early-stage disease is dose and field dependent. Influence of radiation dose on outcome has been examined with a significant benefit seen in patients receiving at least 54 Gy *versus* <54 Gy both in OS and DFS (5-year OS, 75.5% *versus* 46.1%, $p = 0.019$; 5-year DFS, 60.3% *versus* 33.4%, $p = 0.004$) [25]. This is largely due to superior locoregional control, 77% in patients receiving ≥50 Gy, compared to 33% in those treated with less than 50 Gy [39]. Systemic failure is seen in 25–30% of early-stage disease treated with radiotherapy, suggesting a role for chemotherapy added to radiation for control of clinically occult distant disease in high-risk, early-stage patients.

Chemotherapy alone—Few studies have included chemotherapy without radiation because of observations of early disease progression during chemotherapy treatment. A 10-fold worse OS has been reported for patients treated with chemotherapy alone compared to chemotherapy followed by radiation (median survival of 8.8 *versus* 90.3 months) [22]. Studies of chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) without radiation are disappointing because of high rates of refractory or early relapsed disease with CR rates of less than 33%, and 2-year DFS and OS of 23 and 44%, respectively [43,44]. This has been the observation in patients treated with non-anthracycline containing regimens as well [45]. A mechanism postulated for the high failure rate and poor OS with chemotherapy alone is high P-glycoprotein (P-gp) expression in NK lymphoma cells compared to other lymphomas, which results in drug efflux and treatment resistance [46,47]. P-gp expression in *ex-vivo* and *in-vitro* studies is found on $CD56^+$ human NK-cells, as well as in fresh tumor samples from patients with ENKL where expression P-gp/multidrug resistance (MDR) was detected at the initiation of therapy [46,47]. A recent series of 30 patients with early-stage ENKL receiving CHOP with or without a nitrosurea observed an overall CR of 33.3%. However, when stratified by P-gp expression, the CR rate was 60% among patients without expression of P-gp and 20% among patients with

expression of P-gp [41]. Though several studies have confirmed a low response rate to chemotherapy associated with P-gp expression, a recent report describes expression of the short-length (rather than full-length) variant of P-gp in ENKL which does not confer capacity to efflux chemotherapies, including daunorubicin. The clinical impact of short-length variant P-gp in ENKL remains to be studied [41,48,49].

Combined modality therapy—The 5-year OS in early-stage disease with radiotherapy alone has ranged from 29 to >75% depending on the series, leading to continued debate regarding the benefit of adding chemotherapy to radiation (Table II). Combined modality therapy was anticipated to reduce distant failures and overall risk of relapse [50–52]. Promising results were reported in a series of 108 patients with early-stage ENKL receiving radiation followed by combination chemotherapy with cyclophosphamide, epirubicin, vincristine, and prednisone plus bleomycin. This regimen demonstrated significant efficacy with a 92% CR rate and 8-year OS of 86% [30]. Other series have conflicting results with significantly lower OS, 5-year OS of 28–49%, and a wide range of CR rates, 8–78% (Table II) [26,29,31,38,45]. A factor accounting for a portion of this variance is thought to be the sequence of combination therapy, with superior outcomes among studies with up-front radiation *versus* up-front chemotherapy. Collectively, these studies suggest that a subset of patients with high-risk features failed to achieve remission with up-front chemotherapy, translating to a lower OS as patients could not be salvaged with radiation or additional chemotherapy. This is supported by the report of Cheung *et al.* [21] in which only 21% of patients were successfully salvaged with radiation for relapsed disease during anthracycline-based chemotherapy.

Other smaller studies also support the importance of sequence in combined modality therapy. In a series of 63 patients with mostly early-stage disease receiving CHOP chemotherapy followed by 45 Gy of radiation, the CR rate was only 49.1%, compared to 100% in those who received radiation prior to CHOP [29]. In another report, only 6 of 17 patients completed radiation due to early progression during chemotherapy. In this study, patients who completed four cycles of CHOP and planned radiation had an OS rate of 100% compared to 27% among those who did not complete radiation [53]. The final results of JCOG0211, a phase I/II clinical trial in Japan, as recently reported, support the combined modality approach. Twenty-seven patients were enrolled and received 50 Gy of radiation during the first 6 weeks and reduced-dose DeVIC chemotherapy (carboplatin, etoposide, ifosfamide, and dexamethasone) [54,55]. The CR rate was 77% and overall response rate (ORR) 81%. Nine of 10 patients with recurrence following therapy failed at distant sites. In 2006, the International Lymphoma Project review of 136 cases, confirmed the benefit of radiation added to chemotherapy in early-stage disease with a statistically significant survival benefit [56]. Among 280 cases of nasal and extranasal ENKL with stage I disease, radiation-based, combination therapy improved median OS over fourfold (90.3 months *versus* 19.3 months, $p = 0.045$) and PFS almost eight-fold (66.0 *versus* 8.8 months) compared to chemotherapy alone [22].

Collectively, these studies demonstrate that if sequential, combined modality therapy is to be effective in early-stage disease, local control with radiation should precede systemic chemotherapy. Further, the addition of chemotherapy to radiation is likely only necessary in

high-risk, early-stage disease. Prospective trials which stratify patients by low- and high-risk disease are required to determine the additional benefit of chemotherapy in low-risk disease.

Advanced-stage

There is a paucity of data to guide therapy in advanced-stage disease. In general, combined modality therapy is the most commonly employed approach for advanced-stage disease; however, encouraging results with regimens in early-stage disease have not translated to the advanced-stage setting. Further, due to the limited number and size of series which demonstrate a benefit with intensive therapy, it remains unclear whether the superior outcome is due, at least in part, to patient selection. Table III summarizes the experience with chemotherapy. In a small series of 24 patients treated with CHOP or bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, and methotrexate (m-BA-COD) followed by radiation, 25% of patients with advanced-stage disease achieved a CR with OS of 2 months, compared to 75% with early-stage disease with OS of 12 months [57].

Efforts to develop effective regimens for advanced-stage disease have focused on overcoming the MDR-mediated chemotherapy resistance of ENKL with the use of P-gp substrates. Improved outcomes have been achieved with high-intensity chemotherapy combined with radiation. In a study of 32 patients with stage IV, nasal ENKL treated with six cycles of cyclophosphamide, methotrexate, etoposide, and dexamethasone (CMED, with growth factor support) administered every 14 days with radiation (55 Gy to the nasal cavity and nasopharynx) following the third cycle, 21 achieved a CR with a 5-year OS of 65% [63]. Similar efficacy of CMED was reported in another study of 61 patients (97% with stage IV disease), with a CR rate of 80%. At a median follow-up of 46 months, the failure-free survival and OS were 81% and 65%, respectively [59].

Another novel approach is the use of L-asparaginase. L-asparaginase *in-vitro* inhibits tumor cell growth by amino acid deprivation and subsequent inhibition of both protein synthesis as well as DNA and RNA synthesis. *In-vitro*, NK-cell tumors appear highly sensitive to L-asparaginase, as NK cells express low levels of asparagine synthase. As a result of dependence on exogenous asparagine relative to other cells, NK-cell tumors are selectively impacted by this therapy, which has efficacy even in the setting of high-level MDR expression [64]. Efficacy of L-asparaginase was first suggested in 2001 and again in 2003 in two case reports of relapsed ENKL following autologous stem cell transplantation who obtained CRs following 6000 μ/m^2/day of L-asparaginase [65,66]. Subsequently, in a series of 15 patients with relapsed or refractory ENKL treated with L-asparaginase monotherapy, seven achieved a CR, with an ORR of 86.7% [67]. Combination chemotherapy with L-asparaginase, vincristine, and dexamethasone, followed by radiotherapy has been evaluated in patients with refractory disease [60]. Ten of 18 patients (55.6%) achieved a CR, and 5 additional patients achieved a PR with a 5-year OS of 55.6%. This series has been updated with 46 evaluable patients, confirming the initial efficacy data with 51.5% of patients achieving a CR with 5-year OS of 64.5% after failing CHOP chemotherapy and radiation, to which only 28.3% achieved a CR [48]. In yet another series, 18 patients with relapsed or refractory disease received up to six cycles of L-asparaginase-based combination chemotherapy followed by consolidative stem cell transplant. The ORR was 94.4% with

over half, 55.6%, obtaining a CR and 72.2% of patients alive at a median follow-up of 8 months [61].

These concepts have now been integrated into a novel regimen, steroids, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE), which was designed to incorporate L-asparaginase with chemotherapeutic agents known to be independent of MDR. Etoposide was incorporated for its activity in EBV-associated diseases including hemophagocytic syndrome and lymphoproliferative disorders. In a phase I study, six patients were enrolled with stage IV, relapsed, or refractory disease [62]. The first three patients experienced dose-limiting toxicity and one died of sepsis with grade 4 neutropenia, leading to a protocol modification and inclusion of granulocyte colony-stimulating factor (G-CSF). Following this modification, no significant infectious complications occurred. With six patients treated, the reported ORR following two cycles of SMILE was 67% with 50% achieving CR. Three patients received additional SMILE chemotherapy followed by autologous hematopoietic stem cell transplantation. A phase II study of SMILE with G-CSF began in 2007 and is currently ongoing in Asia. These results need to be confirmed in other populations and, if promising, need evaluation in an upfront setting as well.

Hematopoietic cell transplantation

Autologous and allogeneic hematopoietic cell transplantation (HCT) have been evaluated for consolidation, as well as for relapsed or refractory disease. For patients who achieve a CR, autologous HCT may prolong DFS as a consolidative approach, however, only limited studies have directly addressed superiority over conventional therapy. In a case series of 18 consecutive patients with primarily early-stage disease, seven remained in CR following consolidative autologous HCT with follow-up over 5 years (Table IV). Patients in first CR with early-stage nasal disease receiving autologous HCT were compared to historical controls with similar stage and disease status. A non-statistically significant trend toward improved survival was observed for patients with early-stage disease in first CR undergoing consolidative, autologous transplantation [69]. This has now been confirmed in two retrospective reviews including 38 patients, of whom 25 were in CR at time of consolidative HCT [71,72]. The 4-year OS for 22 patients in first CR at time of HCT was 68%, demonstrating a significant benefit compared to 188 historical controls with 4-year OS of 21% [72]. In the second series, nine patients transplanted in first CR were compared to 246 historical controls and demonstrated a statistically significant benefit from autologous HCT [71].

Because of inadequate number of cases reporting outcomes following HCT as salvage therapy, the ability to define its role as therapy for relapsed or refractory disease remains limited. In a series of seven patients with relapsed or refractory disease undergoing autologous HCT, four achieved a CR and median OS was 9 months [71]. The efficacy of this high-dose myeloablative approach either with autologous or allogeneic HCT is limited by a 15% treatment-related mortality and, with 4-year follow-up, OS of only 24% (similar to 21% OS of 188 historical controls) [72]. Since 1996, a total of 43 cases have been reported with salvage HCT in patients with relapsed ENKL, 17 (39.5%) of whom achieved CRs following allogeneic HCT [70,73–77]. In 2000, a successful double-autologous HCT for a

patient with advanced-stage, refractory ENKL was reported [78]. Following a pre-transplant conditioning regimen of high-dose ranimustine, carboplatin, etoposide, and cyclophosphamide followed by high-dose ifosfamide, etoposide, and carboplatin, the patient achieved a CR and remained free of disease after 36 months of follow-up. Despite limited sample size, comparison to historical controls, and potential bias due to patient selection, these studies argue for consideration of autologous HCT for patients in first or second CR, and acknowledging less evidence, for consideration of allogeneic HCT for patients with relapsed or refractory disease. If possible, HCT should be considered in the context of a clinical trial.

Novel approaches under consideration

Uniform expression of surface CD56, neural cell adhesion molecule (NCAM), by NK-cell tumors provides a potential targeted approach. IMGN901 is an immunoconjugate of a cytotoxic derivative of DM1 (*N*-deacetyl-*N*-3-mercapto-1-oxopropyl-maytansine, which inhibits tubule polymerization leading to cell death) conjugated to the antibody, huN901, that binds with high affinity to CD56 [79]. IMGN901 must be internalized after binding to CD56 in order to release DM1. Co-culture of IMGN901 with an NK-cell line results in cell growth inhibition and direct cytotoxicity. A limitation is the lack of specificity to malignant NK-cells as expression of CD56 is seen on benign NK-cells, a subset of T-cells, and within the brain, cerebellum, and at neuromuscular junctions. IMGN901 is currently in human phase I/II clinical trials for ENKL [79].

Other novel therapies have focused on epigenetic modulation of gene expression within the tumor. Preclinical studies of ENKL tumors have observed high levels of aberrant methylation of promoter CpG regions leading to tumor suppressor gene inactivation [80,81]. In 33 patient samples, *p73* was methylated in 94% of cases. Treatment of an *in-vitro* ENKL cell line with 5-azacytidine, a hypomethylating agent, resulted in demethylation and reinduction of *p73* gene expression. Combination therapy trials with hypomethylating agents and histone deacetylase inhibitors which are currently underway in T cell lymphomas are awaited.

Another promising strategy is targeting of EBV, given its role in oncogenesis, in ENKL [82]. An early phase trial of adoptive transfer of EBV-specific cytotoxic T lymphocytes in seven patients has recently been reported [83]. Three patients with nasal ENKL received either transferred autologous EBV-specific, cytotoxic T lymphocytes (CTL) or allogeneic EBV-specific CTLs from an HLA-matched, sibling. One patient achieved a CR, one maintained stable disease, and one died of disease progression after 15 months. Peripheral blood samples assayed during and following CTL infusions confirmed increased EBV-specific lymphocyte populations. A second adoptive transfer strategy used gene transfer to enhance the expression and immunogenicity of LMP2, an EBV-specific peptide, on the surface of antigen presenting cells (APC) [84]. Autologous CTLs were infused into four patients with nasal ENKL as active therapy in one patient and maintenance in three patients following stimulation and expansion in culture with the modified APCs. As active therapy, CTL infusion resulted in a five-fold expansion of LMP2-specific lymphocytes for greater than 3 months and a corresponding fall in the EBV viral load occurred. After 9 months the patient

relapsed and subsequently died at 18 months. All three patients who received maintenance autologous lymphocyte infusions remained in remission for 2–6 months, and post-infusion peripheral blood studies confirmed a five-fold increase in LMP2-specific CTLs.

Conclusion

Though considerable advances have been made in our understanding of NK-cell biology, malignant transformation including the role of EBV, and prognosis, the rare nature of extranodal NK/T-cell lymphoma and its heterogeneity limit the ability to standardize therapy. Without randomized, controlled trials, treatment recommendations are based on review of case series, with their inherent limitations. When possible, every effort should be made to enroll patients in clinical trials and national registries. International, multicenter clinical trials for patients with extranodal NK/T-cell lymphoma are desperately needed to improve outcomes for this rare and aggressive entity.

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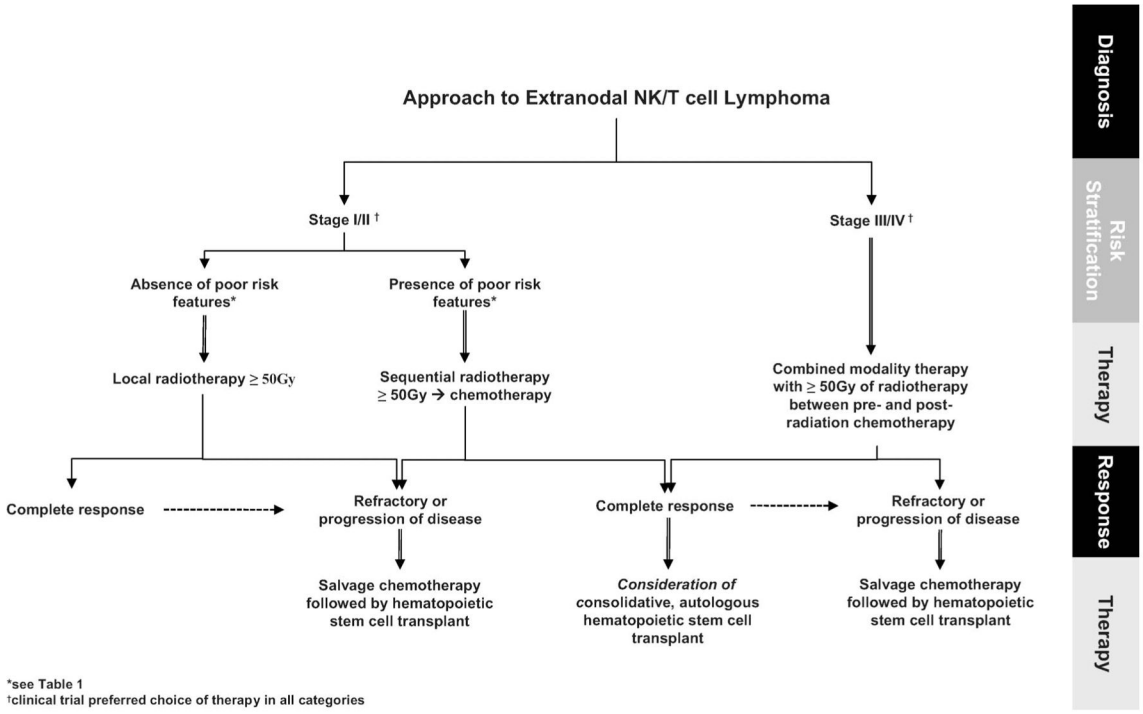

Figure 1.
Diagnostic and treatment approach to extranodal NK/T-cell lymphoma.

Table I

Prognostic factors in extranodal NK/T-cell lymphoma.

		Survival	
Characteristic	**% CR**	**Median survival months**	**% 5y OS**
Age *			
≥65 years	50–61	NR	36–39
<65 years	44–64	NR	33–73
Ann Arbor stage III/IV *			
I	50–86	NR	42–78
II	46–86	NR	19–48
III/IV	23–42	NR	20
B symptoms *			
Present	38–63	NR	19–33
Absent	60–75	NR	41–49
International Prognostic Index			
Low (0–1)	58–92	>10y	57.4 (20y)
Low intermediate (2)		12	27.6 (20y)
Nasal only	50–91		82 (8y)
High intermediate (3)		12	27.6 (20y)
Nasal only	14–92		90 (8y)
High (>3)		4–6	27.6 (20y)
Nasal only	5–90		84 (8y)
NK Lymphoma Prognostic Index †			
Low (0)	NR	>10y	80.9
Low intermediate (1)	NR	30	64.2
Intermediate high (2)	NR	9	34.4
High (3–4)	NR	4	6.6
EBV viral load at diagnosis			
$<6.1 \times 610^7$ copies/mL	NR	>54	80.9
$\leq 6.1 \times 610^7$ copies/mL	NR	2.1	64.2

NR, not reported; y, year; CR, complete remission; OS, overall survival.

*Prognostic significance supported by multiple series including in multivariate analysis.

†Risk factors compose the NK cell lymphoma prognostic index proposed by Lee, *et al*, include Ann Arbor stage, LDH, B symptoms, regional lymphadenopathy [24].

Table II

Treatment and outcome for early-stage extranodal NK/T-cell lymphoma*.

			Outcomes	
Author (year)	***N* (stage I/II)**	**Treatment regimen (*n*)**	**% CR**	**% 5y OS**
Aviles *et al.* (2000) [30]	108 (108)	RT followed by CEOP-bleomycin	92	86 (8y)
Kim *et al.* (2001) [36]	143 (74)	RT (104)	69	35
		CHOP or BACOP followed by RT (39)	8	38
Cheung *et al.* (2002) [21]	79 (79)	Overall	68	38
		RT (18)	NR	29
		CMT(95% anthracycline-based regimen)(61)	NR	40
You *et al.* (2004) [26]	42 (42)	Overall	72	61
		RT (6)	NR	83
		CHOP, CEOP, or m-BACOD(22) ± salvage RT (18)	NR	29
Li *et al.* (2004) [31]	77 (56)	Overall	63	NR
		RT (11)	55	50
		CT(92% CHOP-based regimen)(18)	50	15
		CMT(27)	74	59
Kim *et al.* (2005) [37]	53 (29)	Overall	NR	69
		RT (33)	52	76
		CHOP, EPOCH, or COPBLAM-V + RT(22)	38	59
Li *et al.* (2006) [38]	105 (105)	Overall stage I	87	78
		Overall stage II	NR	46
		RT (31)	97	66
		RT followed by CT (34)	71	77
		CT ± salvage RT (40)	19	74
Isobe *et al.* (2006) [39]	35 (35)	Overall	80	47
		RT (17)	NR	44
		CMT(83% anthracycline-based regimen)(18)	NR	52
Huang *et al.* (2008) [25]	82 (82)	Overall	83	52
		RT (9)	100	90
		CHOP(8)	25	NR
		CMT (65), up-front RT (31), up-front CT (43)	NR	48
Kim *et al.* (2008) [22]	280 (211)	Overall UAT	60	NR
		Overall NUAT	32	NR
		RT (17) or CT + RT (104)	NR	(90.3 month median)
		CHOP, CEOP, or COPBLAM-V(144)	NR	(8.8 month median)
Li *et al.* (2008) [40]	91 (71)	Overall, CMT (64), RT (13) or CT (14) monotherapy	79	65
		Overall stage I	NR	93
		Overall stage II	NR	71
Guo *et al.* (2008) [29]	63 (57)	Overall	NR	70 (2y)
		CHOP (6) or CHOP + RT (53)	49	NR
		RT +CHOP (4)	100	NR

			Outcomes	
Author (year)	***N* (stage I/II)**	**Treatment regimen (*n*)**	**% CR**	**% 5y OS**
Wang *et al.* (2008) [41]	30 (28)	Overall (CHOP or CHOP + nitrosurea)	33	69 (2y)
		Overall P-gp positive	20	NR
		Overall P-gp negative	60	NR

*Y, year; NR, not reported; CT, chemotherapy; RT, radiotherapy; CMT, combined modality therapy (chemoradiotherapy); CR, complete remission; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; UAT, upper aerodigestive tract; NUAT, non-upper aerodigestive tract; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CEOP, cyclophosphamide, epirubicin, vincristine, and prednisone; m-BACOD, mitoxantrone, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; BACOP, bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisolone; EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; COPBLAM-V, cyclophosphamide, doxorubicin, vincristine, prednisolone, bleomycin, procarbazine; P-gp, p-glycoprotein.

Limited to series of at least 30 patients.

Table III

Treatment and outcome for advanced-stage and relapsed or refractory extranodal NK/T-cell lymphoma.

			Outcomes	
Author (year)	***N* (stage III/IV)**	**Treatment regimen (*n*)**	**% CR**	**% 5y OS**
Advanced-stage				
Kwong *et al.* (1997) [57]	24 (4)	CT + RT, stage III/IV	25	(2-month median)
Yong *et al.* (2001) [43]	37 (11)	Overall	NR	43 (2y)
		CHOP	27	NR
		CHOP followed by CMT	46	NR
Kim *et al.* (2003) [44]	59 (18)	CHOP or COPBLAM-V + salvage RT	36	44
Chim *et al.* (2004) [28]	67 (11)	Overall	64	37 (20y)
		Up-front RT (7)	NR	83 (20y)
		Up-front anthracycline-based CT + RT(59)	NR	32 (20y)
Li *et al.* (2004) [31]	77 (21)	Overall	43	NR
		RT (1)	0	0
		CHOP-based regimen(10)	60	30
		RT + CT (10)	30	20
Yong *et al.* (2006) [48]	46 (19)	CHOP +RT	65	65
Lee *et al.* (2006) [45]	26 (10)	IMEP (14) ± salvage RT (12), stage III/IV	13	30 (3y)
Pagano *et al.* (2006) [58]	26 (8)	CT (9), CT + RT (14), CT + surgery (2), surgery (1)	23	18
Aviles *et al.* (2007) [59]	61 (61)	CMED +RT	80	65
Guo *et al.* (2008) [29]	63 (6)	Overall stage I–IV	NR	70
		Overall stage III/IV	NR	50
		CHOP (6) or CHOP + RT (53)	49	NR
		RT + CHOP (4)	100	NR
Li *et al.* (2008) [40]	91 (20)	Overall stage I–IV	79	65
		Overall stage III	NR	36
		Overall stage IV	NR	22
		RT (13)	77	NR
		CT (14)	30	NR
		CHOP or CHOP-bleomycin + RT (46)	85	NR
		RT + CT (18)	89	NR
Relapsed or refractory disease				
Yong *et al.* (2003) [60]	18	L-asparaginase, vincristine, dexamethasone	56	56
Jaccard *et al.* (2008) [61]	18	L-asparaginase, methotrexate, and dexamethasone	56	72 (8-month)
Yamaguchi *et al.* (2008) [62]	6	SMILE	50	NR

Y, year; NR, not reported; CT, chemotherapy; RT, radiotherapy; CMT, combined modality therapy (chemoradiotherapy); CR, complete remission; OS, overall survival; SMILE, steroid dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CMED, cyclophosphamide, methotrexate, etoposide, and dexamethasone; COPBLAM-V, cyclophosphamide, doxorubicin, vincristine, prednisolone, bleomycin, procarbazine; IMEP, ifosfamide, methotrexate, etoposide, and prednisolone.

Table IV

Treatment and outcome for extranodal NK/T-cell lymphoma with hematopoietic cell transplantation.

				Outcomes	
Author (year)	***N***	**Transplant regimen (*n*)**	**Patient characteristics at transplant (*n*)**	**% CR**	**% OS (y)**
Takenaka *et al.* (2001) [68]	3	Auto (2), Allo (1)	SD or PD (3)	67	67 (5y)
Au *et al.* (2003) [69]	18	Auto (18)	CR1 (7), CR2 (5)	58	NR
Murashige (2005) [70]	28	Allo (28)	22 extranodal, CR (8), SD or PD (20)	NR	40 (2y)
Kim *et al.* (2006) [71]	16	Auto (16)	CR1 or CR2 (9), SD or PD (7)	75	71 (2y)
Suzuki *et al.* (2006) [72]	40	Auto (25), Allo (15)	22 extranodal, SD or PD (18)	NR	39 (4y)
			CR (22)	NR	68 (4y)

Y, year; Auto, autologous; Allo, allogeneic; CR, complete remission; SD, stable disease; PD, progression of disease; OS, overall survival; NR, not reported.