Title: **Extranodal natural killer/T-cell lymphoma: an overview on pathology and clinical management**

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Abstract

Natural killer (NK)/T-cell lymphomas arise mainly from NK-cells and occasionally T-cells, and are universally infected with Epstein Barr virus (EBV). They are uncommon lymphomas more prevalent in Asian and Central/South American populations. NK/T-cell lymphomas are clinically aggressive and predominantly extranodal. The most commonly involved sites are the nasal cavity, followed by non-nasal sites including the skin, gastrointestinal tract and testis. The diagnosis of extranodal NK/T-cell lymphoma is established with histological and immunohistochemical examination, together with the demonstration of EBV in the tumour cells. Staging by positron emission tomography computed tomography is essential to inform the optimal management. Plasma EBV DNA quantification should be performed as it serves as a marker for prognostication and treatment response. Survival outcomes of patients with early-stage disease are good following treatment with non-anthracycline based chemotherapy, together with sequential/concurrent radiotherapy. For advanced-stage disease, asparaginase-containing regimens are mostly used and allogeneic haematopoietic stem cell transplantation should be considered for those at high risk of relapse. Salvage chemotherapy is largely ineffective for relapsed/refractory disease, which has a grave prognosis. Novel therapeutic approaches including immune check-point blockade, EBV-specific cytotoxic T-cells, and monoclonal antibodies are being investigated to improve outcomes for those with high risk and relapsed/refractory disease.

Keywords
NK/T-cell lymphoma; Epstein Barr virus; radiotherapy; chemotherapy; immunotherapy

Introduction

Lesions arising from midline facial structures, some inexorably fatal and referred to as lethal midline granuloma, were reported more than seventy years ago [1]. Histologic examination of such cases showed a malignant-looking polymorphic lymphoid infiltration, morphologically described as polymorphic reticulosis [2]. With the advent of immunophenotyping on paraffin-embedded sections, lymphoma cells were found to be CD3-positive and often showed angiocentricity, leading to designation of these lesions as angiocentric T-cell lymphoma [3]. More detailed studies demonstrated that in the majority of cases lymphoma cells exhibit features typical of natural killer (NK)-cells, being negative for surface CD3, but positive for cytoplasmic CD3, CD56, and cytotoxic molecules (perforin, granzyme B, or TIA1); with T-cell receptor (*TCR*) genes in germline configuration and the invariable presence of episomal Epstein Barr virus (EBV) infection [4]. In a minority of cases, lymphoma cells are of T-cell lineage, expressing surface CD3 and with *TCR* genes clonally rearranged [4]. The current World Health Organization (WHO) lymphoma classification designates these lymphomas as NK/T-cell lymphoma to reflect their putative NK-cell or T-cell derivation [5].

Clinical presentations

NK/T-cell lymphomas are found predominantly in Asian and South American countries [4-6], although cases from Western countries are increasingly described [7]. Clinically, NK/T-cell lymphomas are extranodal in distribution. In about 80% of cases, the initial sites involved are the nasal cavity, paranasal sinuses, nasopharynx, Waldeyer's ring and the upper aerodigestive tract. These cases are clinically referred to as the nasal subtype (Figure 1). In about 10–20% of cases, lymphomas occur primarily in the skin, gastrointestinal tract, testicles and salivary glands. They are referred to as the non-nasal subtype (Figure 2). In fact, these non-nasal sites are also where nasal cases may metastasize to initially or terminally (Figure 3). Hence, for patients with diseases presenting in non-nasal sites, appropriate clinical and radiologic examination should be performed to exclude an overt/occult nasal primary. If nasal involvement is found, disseminated nasal NK/T-cell lymphoma should be diagnosed. In view of the frequent disease involvement outside the nasal region, the qualifier "nasal type" used in the previous editions of WHO classification was removed in the 2022 edition. In <5% of cases, lymphomas are disseminated with hepatosplenomegaly, lymphadenopathy, skin infiltration, and marrow involvement. Occasionally, a leukaemia phase may also occur. These disseminated cases are referred to clinically as the aggressive lymphoma/leukaemia subtype [4], and pathologically as aggressive NK-cell leukaemia by the WHO classification [8].

Histopathologic features

The histopathologic features of nasal and non-nasal cases are similar. Lymphoma cells are medium to large in size, admixed with a polymorphic infiltrate of small lymphocytes, plasma cells, histiocytes and eosinophils. There is frequently angiocentricity/angiodestruction, with associated zonal necrosis. Lymphoma cells are typically positive for cytoplasmic CD3, CD56, cytotoxic markers and EBV encoded small RNA (EBER) on in situ hybridization (ISH). Importantly, WHO criteria stipulate that NK/T-cell lymphoma must be positive for EBV, and express either CD56 or cytotoxic molecules. If both CD56 and cytotoxic molecules are negative, the diagnosis becomes EBV-positive peripheral T-cell lymphoma [5].

Four specific clinicopathologic entities must be differentiated from NK/T-cell lymphomas. Plasmacytoid dendritic neoplasms, previously erroneously called blastoid NK-cell lymphomas, are cutaneous CD56+ dendritic cell malignancies that are negative for CD3, cytotoxic molecules and EBV [9]. Indolent NK-cell lymphoproliferative disorder of the GI tract (previously known as NK-cell lymphomatoid gastropathy/NK-cell enteropathy) is a rare

non-neoplastic proliferation of NK-cells in the gut (stomach, and small and large bowels) [10, 11] which is EBV-negative and self-limiting. Chronic lymphoproliferative disorder of NK-cells is uncommon, which is EBV-negative and of uncertain reactive or neoplastic nature [12]. Finally, very rare cases of EBV-negative aggressive leukaemia/lymphoma of putative NK-cell derivation have been described [13]. It is uncertain if they are related to NK/T-cell lymphomas.

Molecular pathology contributing to lymphomagenesis

Genome wide association studies identified three loci, *HLA-DPB1*, *IL18RAP* and *HLA-DRB1*, where base changes leading to amino-acid differences might increase the susceptibility of Asian patients to NK/T-cell lymphoma [14, 15]. HLA-DPB1 is the β1 subunit of the HLA-DP heterodimer, which participates in antigen presentation [14]. IL18RAP (interleukin-18 receptor associated protein) is a subunit of the heterodimeric IL-18 receptor, which may affect the affinity of binding to IL-18, thereby impacting on cell-mediated immunity. HLA-DRB1 is the most prevalent β subunit of the HLA-DR heterodimer. Its changes may affect the peptide-binding pocket of HLA-DR [15]. The link of polymorphisms of proteins affecting immune response with NK/T-cell lymphoma susceptibility suggests that racial predilection might be related to genetic differences in immune control of EBV infection and its putative oncogenic sequelae. Whether similar genetic susceptibilities may be identified in other ethnic populations at risk of NK/T-cell lymphomas remains to be defined.

EBV infection plays a key role in the pathogenesis of NK/T-cell lymphoma, and exhibits a latency II pattern with expression of EBER, LMP2, EBNA1 and BART miRNAs and variable expression of LMP1 [16, 17]. The viral genome is present in a clonal episomal form in tumour cells, indicating infection prior to malignant transformation. The molecular pathways by which EBV, a virus naturally showing a tropism for B cells, can cause malignant transformation in T/NK cells are not fully understood. LMP-1 can induce the expression of NFκB as well as PI3K/AKT, JNK, and p38/MAPK [17]. BART miRNAs can inhibit the tumour suppressor gene adenomatous polyposis coli (APC) and can inhibit an antiviral response through reducing antigen loading by MHC class I [18, 19]. Epigenetic changes can also be induced by EBV including hypermethylation of tumour suppressors and changes in histone structure [20, 21]. Finally, the EBV genome is frequently mutated in NK/T-cell lymphoma with deletion of lytic genes but never EBNA1, EBERs or the early lytic genes BZLF1 or BRLF1 [22], suggesting that abortive lytic replication may be implicated in the pathogenesis of NK/T-cell lymphoma and other EBV-associated lymphoid neoplasms.

Karyotypic studies of NK/T-cell lymphoma have been limited and were mostly performed in cases with marrow infiltration. Consistent alterations include del(6)(q21q25), i(1q), i(7q), +8, del(13q), del(17p) and i(17q) [23, 24]. Frequent chromosomal deletions suggest that putative tumor suppressor genes might be involved, with *HACE1* [25], *PRMD1* [26], *FOXO3* [27] and *PTPRK* [28] implicated in the deleted chromosome 6q. Moreover, activation of putative oncogenes, including *EZH2* [29] and *RUNX3* [30], have also been reported. Gene expression profiling also suggest other oncogenic mechanisms, including MYC and NK-κB over-expression [31], and aberrant JAK/STAT and aurora kinase A activation [32].

With the development of next generation sequencing (NGS), the mutational landscape of NK/T-cell lymphoma has become better defined. Genes mutated included those involved in cellular signaling (*JAK3*, *STAT3*, *STAT5B*) [33-35], epigenetic regulation/deregulation (*BCOR*, *KMT2D*, *ARID1A*, *EP300*, *ASXL3*) [35], tumor suppression (*TP53*, *MGA*) [36], and multiple cellular functions (*DDX3X*) [36].

Other mechanisms that affect gene functions in NK/T-cell lymphomas have also been proposed. Promoter hypermethylation leading to protein down-regulation were reported for *BIM*, *DAPK1*, *SHP1*, *TET2* and *SOCS6* [37]. Micro-RNA down-regulation, including miR-101, miR-26, miR-146a, miR-28-5 and miR-363, which resulted in deregulation of cell cycle-related,

TP53 and MAPK signaling pathways had also been reported [38].

Immune evasion is another mechanism contributing to NK/T-cell lymphomagenesis. There is tumor over-expression of programmed death ligand-1 (PD-L1) [39], the cognate ligand of the immune checkpoint protein PD-1 expressed on T-cells. In NK/T-cell lymphomas, PD-L1 is over-expressed via different mechanisms [40]. The EBV oncoprotein LMP1 activates the NF-κB pathway, which up-regulates PD-L1 expression [41]. Moreover, LMP1 increases the transcription factor AP-1, which drives PD-L1 expression [42]. Finally, the JAK/STAT pathway is often activated in NK/T-cell lymphoma cells, which up-regulates PD-L1 gene expression by interacting with the interferon-stimulated response element located in its promoter [43]. Ligation of PD-L1 on lymphoma cells with PD-1 on T-cells results in inhibition of cell-mediated cytotoxicity, leading to immune escape that contributes to lymphoma cell proliferation.

Molecular pathogenetic features of therapeutic relevance

With a combined genomic and transcriptomic approach, NK/T-cell lymphoma can be classified into three molecular subtypes, TSIM (alteration in Tumour Suppressors and Immune Modulators), MB (*MGA* mutations and loss of heterozygosity at the *BRDT* locus) and HEA (mutations in *HDAC1*, *EP300* and *ARID1A*) [44]. The TSIM subtype, occurring in about 55% of cases, was characterized by mutations in the JAK/STAT pathway and *TP53*, amplifications of the 9p24.1/*JAK2*, 17q21.2/*STAT3*/*STAT5A*/*STAT5B* and 9p24.1/*PD-L1*/*PD-L2* loci, and deletion of chromosome 6q21. Lymphoma cells had a predominant NK-cell gene expression pattern, JAK/STAT pathway activation, PD-L1/2 over-expression and genomic instability. The MB subtype, occurring in about 18% of cases, was characterized by *MGA* mutation and loss of heterozygosity (LOH) of the 1p22.1/*BRDT* locus. Lymphoma cells had gene expression intermediate between NK-cell and T-cell. Mutations of *MGA* led to increased MYC expression, which coupled with *BRDT* LOH resulted in MAPK, NOTCH and WNT pathway activations. The HEA subtype, occurring in about 27% of cases, was characterized by mutations in *HDAC9*, *EP300* and *ARID1A*. Lymphoma cells had a predominant T-cell gene expression pattern, showing over-expression of the histone chaperone DAXX, and activation of the NF-κB and T-cell receptor signaling pathways. From RNA-seq and immunohistochemical results, the TSIM, MB and HEA subtypes could be defined by over-expression of PD-L1, MYC and DAXX respectively. These features are of potential therapeutic implications, which may include immune checkpoint inhibitors for TSIM cases, MYC inhibitors for MB cases, and epigenetic modifiers for HEA cases.

In another recent study that combined nanostring and immunohistochemical analyses, which examined FoxP3, PD-L1 and CD68 expression, NK/T-cell lymphomas were divided into four immune microenvironment subtypes, viz., immune tolerance, immune evasion-A, immune evasion-B and immune silenced [45]. Preliminary results showed that the response to PD-1 blockade might be related to these immune subtypes (1/1 for the immune tolerance group, 3/5 in the immune evasion groups, and 0/5 for the immune-silenced group).

Dysregulation of glutamine metabolism in NK/T-cell lymphoma has been proposed to constitute a metabolic vulnerability [46]. On metabolomic analysis, NK/T-cell lymphoma demonstrated low asparagine synthetase activity, as shown by increase in serum levels of alanine, aspartic acid, glutamine and succinic acid [46]. Owing to low asparagine synthetase activity, such lymphoma cells are susceptible to asparaginase treatment. These observations suggest that asparagine synthetase might be a biologic marker of treatment response and prognosis [47]. The protein excitatory amino acid transporter 3 (EAAT3) encoded by *SLC1A1* had been identified as an extracellular glutamine transporter, which mediated cellular glutamine uptake, thereby inducing glutamine addiction. Furthermore, EAAT3 also down-regulated PD-L1. Targeting EAAT3-mediated glutamine addiction with asparaginase would

therefore be therapeutically relevant [48].

Evaluation and prognostication of patients with NK/T-cell lymphoma

The diagnosis of NK/T-cell lymphoma requires a biopsy of the lesion with detailed histological examination including immunohistochemistry to characterize the abnormal lymphoid cells. Typically, the lymphoma cells are positive for CD3, CD56 and cytotoxic markers such as TIA1 [5]. In situ hybridization (ISH) for EBER should be performed as a highly sensitive and specific method to demonstrate the presence of EBV [5]. Staging by 18-fluorodeoxyglucose (FDG) positron emission tomography computed tomography (PET/CT) is the recommended imaging modality because NK/T-cell lymphomas are moderately FDG-avid [49, 50]. The use of CT imaging alone may miss subtle lymphoma involvement outside the primary site, resulting in advanced-stage lymphoma being under-staged and managed as early-stage disease [51]. As PET/CT has insufficient sensitivity for detecting bone marrow involvement, ISH for EBER in bone marrow biopsy samples is mandatory. Quantification of circulating cell-free plasma EBV DNA provides an objective measurement of the tumour load and also serves as a marker for prognostication, treatment response assessment, and surveillance for early lymphoma recurrence [52-54].

Various prognostication models have been used for NK/T-cell lymphoma. The earlier models such as the International Prognostic Index (IPI) and the Korean Prognostic Index (KPI) were derived from patient cohorts treated with anthracycline-based regimens now considered inadequate for NK/T-cell lymphomas [55, 56]. The most well validated model for patients treated with non-anthracycline-based protocols is the prognostic index for NK/T-cell lymphomas (PINK) [57]. There are four poor risk-parameters included in PINK: age >60 years, stage III/IV, presence of distal nodal involvement, and non-nasal disease subtype. The addition of detectable EBV DNA as another parameter to PINK (PINK-E) further stratifies patients into different prognostic groups that portend different survival outcomes [57]. More recently, the nomogram-revised risk index (NRI) was devised to stratify patients into different risk groups based on age, stage, performance status, lactate dehydrogenase (LDH) level and primary tumour invasion [58]. For early stage disease, it appears that there is a better separation between different risk groups using NRI as compared with PINK.

Management of patients with NK/T-cell lymphoma

NK/T-cell lymphoma cells express multidrug resistance 1 (MDR-1) and its gene product P-glycoprotein [59]. EBV-infected T/NK cells are intrinsically resistant to apoptosis due to over-expression of the antiapoptotic molecules BCL-XL and MCL-1 [60]. Modern chemotherapy protocols use drugs that are not impacted by MDR-1, such as etoposide or ifosfamide [61]. NK/T-cell lymphoma is sensitive to radiotherapy (RT) when delivered at doses typically >50 Gy. Omitting RT in early-stage disease is associated with poor outcomes [62]. As a result of glutamine addiction, NK/T-cell lymphoma is also vulnerable to asparagine depletion that triggers apoptosis, providing a rationale for incorporating asparaginase in therapeutic protocols [63].

Treatment for early stage disease

Evidence supporting management approaches of early-stage NK/T-cell lymphoma is largely based on non-randomised phase I/II trials and retrospective reviews, limiting direct comparisons between different strategies (Table 1). Treatment protocols vary with respect to dose and type of agents employed, and sequencing with radiotherapy. Toxicity profiles also differ and, in particular, there are scarce data to guide the management of older patients with co-morbidities. Asparaginase is included in many protocols for early-stage disease. However,

a recent retrospective multicentre propensity-matched study has apparently shown comparable overall survival (OS) rates between regimens with and without asparaginase [64].

Role of radiotherapy for early stage disease

In early-stage disease, a perennial question is whether RT alone is sufficient, or combined RT and chemotherapy is necessary for all patients A retrospective review of 1276 patients from 10 Chinese institutions evaluated RT as a single modality and sequential or concurrent chemotherapy and RT [62]. Among a study-defined low-risk group of patients with no evidence of local tumour invasiveness, RT alone was associated with a 5-year OS of 88.8%, with no apparent additional benefit from chemotherapy. In high risk patients, RT followed by chemotherapy was associated with better outcomes. However, 81% of patients in this study received anthracycline-based chemotherapies now considered ineffective for NK/T-cell lymphomas. PET-CT and circulating EBV DNA quantification were also not used in risk-stratification, making the definition of low-risk patients unclear [65]. There are no prospective data applying established risk scores to guide which patients might be successfully managed with RT alone.

Owing to heterogeneous protocol designs, the optimal timing of radiotherapy in relationship to chemotherapy remains unclear. A retrospective analysis of 303 patients treated with non-anthracycline regimens showed no effect of sequential versus concurrent RT on complete remission (CR) rate, progression free survival (PFS) or OS [66]. Another study showed a benefit of sequential sandwich chemotherapy and RT versus concurrent use of chemotherapy and RT in terms of CR rate and PFS but not OS. However, this study was confounded by the GELOX regimen being used in the sandwiched radiotherapy protocols, but ineffective anthracycline-based regimens in other groups [67]. Another study that employed GDP as the chemotherapy backbone found that RT followed by chemotherapy was superior to chemotherapy followed by RT in terms of PFS (5-year PFS: 81.6% vs. 56.0%, $p = 0.017$) but not OS [68].

The mode of radiotherapy appears to be important, intensity-modulated radiotherapy (IMRT), as compared with 3-dimensional conformal radiotherapy, resulted in comparable CR rates and safety, but better OS (75.9% *vs* 68.9% p=0.004) and PFS (67.6% *vs* 58.2% p<0.01). Receipt of >54 Gy radiotherapy has been associated with more favourable prognosis and is recommended by guideline groups [61, 69]. Notably however, a retrospective study suggested that lower doses (median 46 Gy) can be safely used in those patients who achieve CR after induction chemotherapy [70].

Concurrent chemotherapy and radiotherapy for early stage disease

In concurrent chemotherapy and RT, RT controls the local disease whilst chemotherapy serves both as a radiosensitizer and reduces the risk of systemic relapse. One of the best-studied regimens is DEVIC plus 50 Gy RT, and in a small prospective phase I/II study, this approach conferred a 2-year OS of 78% [71]. Grade 3 mucositis was observed in 30% of patients. Other approaches have used cytotoxic agents as radiosensitizers concurrently during RT, followed by a more intensive chemotherapy consolidation. In a phase 2 study, cisplatin was given concurrently with 40-52.8 Gy RT followed by 3 cycles of VIPD [72]. The CR rate was 80% with a 3-year OS of 86.28%. However, febrile neutropenia occurred in 60% of cases, with a treatment-related mortality (TRM) of 7%. A similar approach utilized 36-44 Gy radiotherapy with concurrent cisplatin and asparaginase, followed by two cycles of MIDLE, resulting in a 3-year OS of 81.5% [73]. In a prospective study examining concurrent RT and pegylated asparaginase in patients, the CR rate was 100% with a 2-year OS of 90.9% [74]. The regimen was also well tolerated. However, 27 of 30 patients in this study had low-risk PINK score; hence these data cannot be applied to high-risk patients.

Sequential chemotherapy and radiotherapy for early stage disease

The practicalities of delivering timely radiotherapy for newly-diagnosed patients is challenging. In most centers, chemotherapy followed by radiotherapy is logistically easier, with the added advantage of obviating the toxicity typically associated with concurrent radiotherapy and chemotherapy.

In one study of 18 patients, two cycles of modified SMILE followed by 45 Gy radiotherapy resulted in a CR rate of 88.9% and a 5-year OS of 72% [75]. However, 75% of patients developed grade 3/4 haematological toxicity and other serious adverse events included neutropenic fever and acute kidney injury. In another retrospective single-centre study of 33 patients, sequential DICE-L-asparaginase followed by 45 Gy radiotherapy resulted in a CR rate of 90%, with a 5-year OS of 82.9% [76]. Febrile neutropenia was experienced by 27% of patients

Chemotherapy with sandwiched radiotherapy is another approach. In a prospective study, two cycles of GELOX, followed by 56 Gy RT and consolidated with another 2-4 cycles of GELOX resulted in a CR rate of 74% and a 2-year OS of 86% [77]. Grade 3/4 haematological toxicity was seen in a third of patients with only a small proportion experiencing non-haematological severe toxicities. In another study of 66 patients receiving the regimen LVDP and sandwiched radiotherapy of 56 Gy concurrent with cisplatin, a CR rate of 83.3% and a 3-year OS of 70.1% were observed [78]. Five patients experienced grade 3 mucositis or dermatitis related to radiation.

Treatment for advanced stage disease

Outcomes of patients with advanced NK/T-cell lymphoma were historically poor with CHOP-based regimens [79]. Data from a range of studies in advanced stage disease are summarised in Table 2. The best-tested regimen is SMILE, an intensive regimen that combines asparaginase with chemotherapeutic agents that are MDR-independent [80]. A 5-year OS of 45% was described in the phase II study [81]. However, grade 3/4 infections were seen in 62% and the TRM rate was 2/38 (5%). These data have been reproduced in real world studies; with a CR rate of 65% and a 5-year OS of 47.4% achieved in newly diagnosed patients [82]. Reported toxicities were similar to the phase II trial; but TRM was still of 7% mainly due to infection. Notably, only 20% of patients achieving CR subsequently experienced relapse [82].

The DDGP regimen was developed using similar rationale whilst attempting to reduce toxicities. A randomized trial was conducted to compare SMILE and DDGP in 87 patients [83]. Patients randomized to the DDGP arm had a superior outcome with a 5-year OS of 74.3%, as compared with 51.7% in the SMILE group. TRM was 2.5% for DDGP but surprising high at 17.5% for SMILE. Furthermore, the OS of SMILE-treated patients appeared also inferior to that previously reported. Hence, it remains unclear whether DDGP is indeed superior to SMILE.

Other treatment approaches for advanced stage NK/T-cell lymphoma have been explored in small single-arm studies. Aspa-Met-Dex was studied prospectively in 19 patients with relapsed/refractory NK/T-cell lymphoma, resulting in a CR rate of 57.9% but a median survival of only 12.2 months [84]. This regimen was generally well tolerated with febrile neutropenia in 10.5% of patients. Notwithstanding the fact that prospective data are in the relapsed/refractory setting, this approach can be considered a reasonable first line option in older, frailer patients [61]. The P-GEMOX regimen showed a CR rate of 42.1% and a 2-year OS of 64.7% in newly diagnosed patients [85].

Haematopoietic stem cell transplantation for NK/T-cell lymphoma

Due to a high risk of relapse beyond CR1 in advanced stage NK/T-cell lymphoma, remissions are often consolidated with high-dose therapy and haematopoietic stem cell

transplantation (HSCT). Unfortunately, the evidence-base is relatively weak. Most data are retrospective or from single-arm studies and there are few data to inform if an autologous or allogeneic approach should be adopted. HSCT was used as consolidation in the initial trials of SMILE. In the initial phase II study, of 28 cases completing two cycles of therapy, seven patients received chemotherapy alone, four patients underwent autologous HSCT and 17 allogeneic HSCT [81]. No statistically significant improvement in OS and PFS was seen in patients receiving autologous HSCT. In a trial recruiting 27 patients with stage IV NK/T-cell lymphoma with a planned autologous HSCT after SMILE induction, sixteen patients did not proceed to transplantation due to either lack of response or toxicity [83]. Outcomes were superior for those undergoing autologous HSCT but the results might be confounded by inherent selection-bias.

In a prospective cohort of 27 patients undergoing autologous HSCT, EBV PCR positivity or a Deauville score (DS) of 3-5 on PET-CT pre-HSCT were associated with poor outcomes in a multivariable model [86]. Three-year OS was 67% in the favourable risk group (pre-HSCT DS of 1–2 and negative for EBV DNA) and 29% in the unfavourable group. A multicentre study of 62 patients undergoing first-line autologous HSCT as consolidation reported a 3-year OS of 52.3% in those with advanced disease (n=31) [87]. The achievement of a partial response prior to HSCT was associated with inferior PFS (hazard ratio HR, 4.12; (95% confidence interval CI, 1.90 to 8.91) and OS (HR, 3.22; 95% CI, 1.15 to 8.98). Similar outcomes were reported in a European registry study of 28 patients who had received a median of two prior lines of therapy, with a 2-year OS of 52% and non-relapse mortality (NRM) of 11% [88]. However, these patients were treated from 2000 to 2009, with only 50% receiving a platinum-containing regimen and 21% receiving asparaginase. Thus, the relevance of these data in the context of modern chemotherapy protocols remains unclear. The evolving landscape of first-line therapy and increasing use of PET/CT for response assessment, must be carefully considered when extrapolating the outcomes from historical studies. For example, a retrospective propensity-matched study described a benefit of autologous HSCT in patients with high-risk disease in CR1 [89]. However, this would need to be validated in the modern treatment era.

A large registry study of NK/T-cell lymphoma patients undergoing allogeneic HSCT (n=82) reported a 3-year OS of 34% with a NRM of 30%. Additionally, 42% of patients relapsed, although no relapses were reported after two years [90]. Amongst this cohort the median number of prior lines of therapy was two, with 30% of cases undergoing allogeneic HSCT as part of first line therapy. Only 45% of patients were in CR at the time of transplantation. Remission status at the time of transplantation and conditioning intensity was not associated with relapse risk or OS. In an Asian cohort of 18 patients with advanced stage disease undergoing allogeneic HSCT in CR1 or CR2, the 5-year OS was 57%. Five patients died of infection although in one case this followed relapse and salvage chemotherapy [91].

Interpretation of data from studies of allogeneic HSCT is challenging given the small sample size and heterogeneity in both the conditioning regimens and types of donors. Nevertheless, allogeneic HSCT appears capable of delivering long-term remission in a proportion of patients with high risk and/or relapsed disease, although relapse remains a problem and rates of NRM are high. More data are required to inform decisions on who will benefit most from HSCT and whether autologous or allogeneic HSCT is most appropriate based on disease risk stratification, patient fitness and donor type.

Treatment for relapsed/refractory disease

Patients with relapsed/refractory disease have a dismal prognosis. Salvage chemotherapy is largely ineffective, especially for patients failing prior asparaginase-based regimens. Consequently, immunological based therapies including cellular therapy have been

examined in these high-risk patients (Table 3). Key molecules in NK/T-cell lymphoma cells have been identified as potential therapeutic targets, including EBV antigens, programmed cell death-ligand1 (PD-L1), and CD38.

Given the type 2 latency EBV infection in NK/T-cell lymphoma cells, EBV-related antigens or peptides presented in conjunction with HLA molecules represent attractive targets for immunotherapy [92]. Autologous EBV-specific cytotoxic T-cells (CTL) have been generated to target EBV-associated cancer cells. One such product, baltaleucel-T, was recently examined in a phase II multicenter clinical trial for advanced or relapsed/refractory NK/T-cell lymphomas [93]. Five of ten treated patients responded, with CR achieved in three cases. The median PFS was 12.3 months. Toxicities associated with baltaleucel-T were minimal and there was no cytokine release syndrome reported. However, because product preparation took more than three weeks, >70% of patients recruited progressed during this period and could not receive treatment, representing a major limitation of this strategy.

PD-1 is an immune checkpoint molecule expressed on T-cells, which upon binding to its ligands PD-L1 or PD-L2, delivers inhibitory signals that lead to T-cell tolerance and evasion against foreign and self-antigens. Conceptually, blocking the interaction between PD-L1 on tumour cells and PD-1 on T-cells could direct the tumor microenvironment from a state of immune evasion to immune surveillance. Owing to constitutive PD-L1 over-expression in EBV-infected NK/T-cell lymphoma cells [94, 95], anti-PD-1 antibodies (pembrolizumab, nivolumab, sintilimab, and tislelizumab) and anti–PD-L1 antibodies (avelumab and CS1001) have been investigated in relapsed/refractory diseases. In heavily pretreated patients with NK/T-cell lymphoma, the use of anti-PD-1 antibodies have been shown to be highly effective, with ORRs ranging from 31.8 to 100% (Table 3) [96-103]. Although PD-L1 expression in tumor tissue might be used as a promising biomarker, a cut-off value by immunohistochemical staining to predict treatment response remains to be determined [94].

Strong CD38 expression on NK/T-cell lymphoma has been shown to be a poor prognostic marker [104]. A phase 2 study evaluating the efficacy of daratumumab, an anti-CD38 monoclonal antibody, was conducted for relapsed/refractory NK/T-cell lymphomas. Among 32 patients treated with daratumumab, the ORR was 25% with all responders achieving PR only. The duration of response was short and the median PFS was merely 53 days [105]. Although the efficacy of daratumumab monotherapy was disappointing, it has been suggested that novel combination treatment might improve its efficacy because daratumumab potentially modulates immune effector cells and antibody-dependent cellular cytotoxicity (ADCC) [106].

CD30 is expressed in approximately 40% of NK/T-cell lymphoma and hence considered a therapeutic target [107, 108]. A phase 2 study has been conducted to evaluate the efficacy and safety of brentuximab vedotin (BV), an anti-CD30 monoclonal antibody immunotoxin conjugate in relapsed/refractory peripheral T-cell lymphomas (PTCLs), including NK/T-cell lymphomas [109]. In seven patients with relapsed/refractory NK/T-cell lymphoma, ORR was 29% (CR, n=1; PR, n=1). The duration of response was short. Data on CD30 expression and correlation with response were not presented.

In summary, although immunotherapeutic targeting has been demonstrably well tolerated for relapsed/refractory NK/T-cell lymphomas, the overall efficacy of individual approaches differs widely. Nevertheless, the concept of targeting cellular or viral surface antigens provides an opportunity for future combinatorial studies with focus on immunotherapy and modulation of the tumor microenvironment. Synergistic approaches of immunotherapy combinations or immunotherapy-chemotherapy combinations should be explored in well-designed prospective studies.

Concluding remarks

Historically, when patients with NK/T-cell lymphomas were managed the same way as aggressive B-cell lymphomas with anthracycline-based chemotherapy, outcomes were very poor. For early stage disease, the use of concurrent or sequential chemotherapy (non-anthracycline-based with or without asparaginase) and radiotherapy has led to favourable outcomes with ORR of 80-90% and 5-year PFS rates of 60-70%. There may be a proportion of low-risk early-stage disease patients who could be cured with radiotherapy alone, but there are no prospective data to reliably identify these patients and recurrence remains a concern. For patients with advanced-stage disease treated with asparaginase-based protocols, an ORR of 60-90% and a 5-year PFS of 40-60% can be achieved. On the other hand, the most optimal treatment for relapsed/refractory disease remains to be defined. Novel immunological therapies such as immune checkpoint blockade appear to be promising. Further studies on combination treatment with immunotherapies, specific targeting agents and chemotherapy are warranted to further improve the outcomes of patients with this uncommon and aggressive lymphoma.

Author contribution

All authors were involved in the writing and approval of the manuscript.

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Figure legends

Figure 1. A typical case of nasal NK/T-cell lymphoma presenting with nasal symptoms. On positron emission tomography computed tomography (PET/CT), hypermetabolic lesions were only found in the nose and nasal cavities. Clinically, the nasal lymphoma had caused a perforation of the hard palate, leading to a communication between the nasal and oral cavities, a condition conventional referred to as a lethal midline granuloma. Note that the palatal perforation was not intensely hypermetabolic on PET/CT, suggesting that it resulted from ischemic necrosis due to angioinvasion and angiodestruction from the surrounding lymphoma, instead of direct lymphoma infiltration.

Figure 2. A typical case of non-nasal NK/T-cell lymphoma presenting with cutaneous symptoms. There was extensive cutaneous infiltration and ulceration in the whole body. Lesions were hypermetabolic. Note that on PET/CT, asymptomatic hypermetabolic lesions were also found in the nasal cavity, which on biopsy was shown to be lymphomatous.

Figure 3. NK/T-cell lymphoma presenting with both nasal and non-nasal symptoms. On presentation, there was left nasal blockage and discharge, together with a left buttock skin lesion. Both sites were hypermetabolic on PET/CT, and shown by biopsy to be involved by lymphoma. Such cases blur the distinction between nasal and non-nasal subtypes, if the primary symptomatic/presentation site is the criterion used to classify them

Table 1- Treatment of early stage NK/T-cell lymphoma

Regimen	Chemotherapy agents	Study design	Study population	Outcomes	toxicity
Sequential					
CHOP (4-8 cycles) followed by 56 Gy IFRT[110]	Cyclophosphamide, doxorubicin, vincristine, prednisolone	Retrospective. N= 135	IE/IIE	CR 69.6% 5-year OS 48%	1 TRM (neutropenic sepsis)
CHOP-L (4-6 cycles) + 40-60 Gy RT[111]	Cyclophosphamide, doxorubicin, vincristine, prednisolone, L-asparaginase	Prospective phase II N=38	Stage I/IIE (N= 31) Stage III/IV (N= 7)	CR 28/31 in early stage. 2-year OS 80.1%	Grade 3/4 haematological toxicity 32/38 Neutropenic sepsis 8/38 No TRM
mSMILE (2 cycles) followed by 45 Gy IMRT in stage IE/IIE [75]	Dexamethasone, methotrexate, ifosfamide, peg-asparaginase, etoposide	Retrospective n=28	Stage I/IIE (N= 18) Stage III/IV (N= 7)	CR 16/18 in early stage. 3-year OS 94%	Grade 3/4 haematological toxicity 17/28. Grade 3/4 non-haematological toxicity in 9/28. No TRM
DICE + L-asparaginase followed by 37-46.5 Gy RT[76]	Dexamethasone, etoposide, ifosfamide, l-asparaginase	Retrospective n=33 compared to historical control receiving RT alone n=45	Stage IE/IIE	CR 30/33. 5-year OS 82.9%. RT alone associated with systemic relapse in 11/45 and 5-year OS of 44.4%	Grade 3/4 haematological toxicity 25/33. Grade 3/4 mucositis 2/33.
Sandwich					
GELOX (2 cycles) then 56 Gy RT then GELOX (2 cycles)[77]	Gemcitabine, oxaliplatin, l-asparaginase	Prospective n=27	IE/IIE	CR 20/27. 2-year OS 86%	33% grade 3/4 haematological toxicity. Grade 3/4 mucositis and dermatitis in 14.8% and 11.1%. No TRM
LVDP (2 cycles) then 56 Gy RT with cisplatin then LVDP (2 cycles)[78]	L-asparaginase, etoposide, cisplatin, dexamethasone	Prospective n=66	IE/IIE	CR 55/66. 3-year OS 70.1%	Grade 3/4 haematological toxicity in 16.7%. Grade 3/4 mucositis in 6.1% during RT
LVP (2 cycles) then 56 Gy RT then LVP (2-4 cycles)[112]	L-asparaginase, vincristine, prednisolone	Prospective phase II n=26	IE/IIE	CR 21/26. 2-year OS 88.6%	Grade 3 haematological toxicity in 2/26. No grade 4 toxicities or TRM
Concurrent					
40-52.8 Gy RT with cisplatin followed by VIPD (3 cycles)[72]	Etoposide, ifosfamide, cisplatin and dexamethasone	Prospective phase II n=30	Phase IE/IIE	CR 25/30. 3-year OS 86.28%	Grade 3 toxicity during RT, N=1. Grade 3/4 haematological toxicity during CT 14/29. TRM N=2

40-44 Gy RT with cisplatin followed by VIDL (2 cycles)[113]	Cisplatin given only during RT. etoposide ifosfamide, dexamethasone, l-asparaginase.	Prospective phase II n=30	Phase IE/IIE	CR 26/30. 5-year OS 60%.	Grade 3/4 haematological toxicity in 24/30. Grade 3/4 stomatitis in 6/30. No TRM
DeVIC (3 cycles) + 50 Gy IFRT[71]	Dexamethasone, etoposide, ifosfamide and carboplatin	Prospective phase I/II n=33	IE/IIE	CR 20/27 in phase II arm. 2-year OS 78%	Grade 3 mucositis in 30%. Grade 3/4 neutropenia in 25/27
Peg-asparaginase + 50 Gy RT[74]	Peg-asparaginase	Prospective n=30	IE/IIE	CR 30/30. 2-year OS 90.9%	Grade 3 haematological toxicity in 4/30.
36-44 Gy RT with cisplatin and asparaginase then MIDLE (2 cycles) [73]	Cisplatin, l-asparaginase, methotrexate, etoposide, ifosfamide,	Prospective phase II n=30	IE/IIE	CR 82.1% 3-year OS 81.5%	Grade 3/4 haematological toxicity in 21/23 receiving MIDLE. Grade 3 mucositis 1/30. N=1 TRM
40 Gy RT with cisplatin then sequential VIPD + VIDL +MIDLE[114]	Cisplatin, etoposide, ifosfamide, dexamethasone, l-asparaginase	Prospective phase II n=62	IE/IIE	CR 56/62 3-year OS 83.1%. In-field relapse 6/10	Grade 3/4 non-haematological toxicity 3/62

Table 2- Treatment of advanced stage NK/T-cell lymphoma

Regimen	Chemotherapy used	Study design	Study population	Outcomes	toxicity	Consolidation
Aspa-Met-Dex (3-6 cycles)[84]	L-Asparaginase, methotrexate, dexamethasone	Prospective phase II	R/R	CR 11/19. Median survival 12.2 months	Grade 3/4 haematological toxicity 8/19. 2/19 febrile neutropenia	BEAM ASCT in 5/19
SMILE[81]	Dexamethasone, methotrexate, ifosfamide, l-asparaginase, etoposide	Prospective phase I/II	N=20 newly diagnosed stage IV. N=18 R/R	First line CR 8/20. 1-year OS first line 45%	Grade 4 neutropenia 92%. Infection 61%. TRM 2	ASCT 4/28 alloSCT 17/28
SMILE[82]	Dexamethasone, methotrexate, ifosfamide, l-asparaginase, etoposide	Retrospective real world	N=43 Newly diagnosed. N=44 R/R. All stages with 54% stage IV	CR 28/43 newly diagnosed. 5-year OS 47.4%	Grade 3/4 neutropenia 57/87. TRM 5.	ASCT N=14 alloSCT N=10 RT N=19
SMILE + upfront ASCT [115]	Dexamethasone, methotrexate, ifosfamide, peg-asparaginase, etoposide	Retrospective	N=27 Stage IV disease	CR 9/27 with 9/27 alive at median 28.4 months	TRM 5/27 due to neutropenic sepsis.	ASCT N=11
SMILE v DDGP [83]	Dexamethasone, methotrexate, ifosfamide, l-asparaginase, etoposide or dexamethasone, gemcitabine, cisplatin, peg-asparaginase	Prospective randomised	N=87 1:1 randomisation 80 patients received treatment.	CR 27/40 v 19/40 and 5-year OS, 74.3% vs 51.7% in DDGP v SMILE respectively	TRM 7/40 SMILE. TRM 1/40 DDGP. Grade 3/4 neutropenia 85% SMILE 65% DDGP	Not reported
P-GEMOX[85]	Peg-asparaginase, gemcitabine, oxaliplatin	Retrospective	N=19 newly diagnosed. N=16 R/R	CR 8/19- and 2-year OS 64.7% in newly diagnosed	Grade 3/4 haematological toxicity 14/35 No TRM	ASCT N=7

Table 3. Immunotherapies for relapsed/refractory NK/T-cell lymphoma

Target	Chemotherapy, (Study style)	No. patients	Dose	No. previous CTx median (range)	ORR, % (responders/total)	Grade III or IV toxicities	Biomarker to predict response	Survival outcome	Ref
Autologous EBV-specific T-cell	Baltaleucel-T (Phase II)	15 received (among 47)	2×10^7 autologous $CD3^+$ T lymphocyte cells/m^2	2 (2-6)	46.7% (7/15)	Cough 13.3% Oral pain 13.3% Vomiting 6.7%	EBV DNA (controversial)	mPFS 3.9 mo Responder vs. non : 12.3 vs. 1.8 mOS: NR Responder vs. non : NR vs. 4	[93]
PD-1	Pembrolizumab (Retrospective)	7	2 mg/kg IV, Q3W	7 (2–13)	100% (7/7)	No grade III/IV AEs (Gr 2 rash:100%)	Strong PDL1 expression was likely to show a higher response rate	NA	[96]
PD-1	Pembrolizumab (Retrospective)	7	NA	4 (2–18)	57.1% (4/7)	Thrombocytopenia: 14.3% Neutropenia: 28.6% (Any grade: 71.4%)	No correlation between response and PD-L1 expression	NA	[99]
PD-1	Pembrolizumab (Retrospective)	14	Fixed-dose 100 mg IV, Q3W	2 (1–19)	44% (6/14)	No grade III/IV AEs (Gr 2 rash: 7.1%)	Suggesting the association of EBV-positivity with PDL1 expression	NA	[100]
PD-1	Nivolumab (Retrospective)	3	40 mg IV, Q2W	1	100% (3/3)	NA	NA	NA	[101]
PD-1	Sintilimab (Phase II)	28	200mg IV, Q3w	3 (1–4.5)	75% (21/28)	Lymphopenia:7.1% Respiratory infection: 3.6% Thrombocytopenia: 3.6%	NA	1-year OS: 82.1% 2-year OS: 78.6%	[102]
PD-1	Tislelizumab (Phase II)	Cohort 1: 22	200mg IV, Q3W	2 (1-5)	31.8% (7/22)	Skin adverse reactions: 13.6%	NA	mPFS: 2.7 mo mOS: 8.8 mo	[103]
PD-L1	Avelumab, (Phase II)	21	10 mg/kg IV, Q4W	NA	38% (8/21)	Neutropenia: 10% Fatigue: 5% Infusino reaction: 5%	High Expression of PD-L1 in tumor tissue is likely to mean immunogenic subtype.	mPFS: 2.7 mo mOS: NR	[98]
PD-L1	CS1001 (Phase II)	29	1200 mg IV, Q3W	2 lines: 8(27.6%) ≥3 lines: 6(20.7%)	44% (11/25)	All grade ≥3: 10.3%	NA	NA	[97]
CD38	Daratumumab, (Phase II)	32	16 mg/kg IV Q4W C1-2: D1,8,15,22 C3-6: D1,15 C7~: D1	2 (1-8)	25% (8/32))	Thrombocytopenia: 25% Neutropenia: 18.8% Leukopenia: 15.6% Anemia: 15.6% Pyrexia: 12.5%	No clear trend between baseline CD38 expression and response to daratumumab.	mPFS: 1.8 mo mOS: 4.7mo	[105]
CD30	Brentuximab Vedotin, (Phase II)	7 NK/T-cell lymphomas among 33 PTCLs	1.8 mg/kg IV, Q3W	Less than 3 times: 72.7% (Among 33)	29% (NK/T-cell lymphoma, 2/7)	Neutropenia: 30.3% Thrombocytopenia:18.2% (Among 33)	EBV positivity and CD30 expression were not significantly associated with response.	mPFS: 1.9 mo mOS: 6.1 mo (Among 33)	[109]

± Abbreviation: No, number; CTX, chemotherapy; ORR, overall response rate; mo, months; mPFS, median progression-free survival; mOS, median overall survival; NA, not assessed; NR, not reached; Non, non-responder; Gr, grade; NR, not reached.