Review Article

Extranodal natural killer/T cell lymphoma: we should and we can do more

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Abstract: Extranodal natural killer/T cell lymphoma, nasal type (ENKL) is a rare disease, which is much more prevalent in Asia. With the advent of L-asparaginase-based regimen, the outcome of ENKL was improved obviously. Sequential chemotherapy and radiotherapy is the standard treatment for early-stage ENKL. However, the outcome of advanced-stage diseases is not satisfactory. Therefore, risk-stratification is needed for ENKL. The prognostic factors include IPI, KIPI, plasma EBV-DNA, and interim-PET/CT. However, these parameters are not validated in the era of L-asparaginase. The role of high-dose chemotherapy and heamatopoietic stem cell transplantation require further investigation.

Keywords: Lymphoma; natural killer/T (NK/T); prognosis; chemotherapy; radiotherapy; transplant

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Introduction

Natural killer (NK) cell malignancies are categorized as extranodal NK/T cell lymphoma, nasal type (ENKL), and aggressive NK cell leukemia in the current World Health Organization Classification (1,2). This article is limited to ENKL, which is rare, but much more prevalent in Asia than in Western countries. ENKL is the most common peripheral T-cell lymphoma (PTCL) in Aisa, accounting for 22.4% of PTCL (3,4). ENKL occurs predominantly in the nasal, paranasal and oropharyngeal sites. Some of them are located in the skin, gastrointestinal tract, and testis (5,6). Histologically, ENKL shows an angiocentric or angiodestructive growth pattern with small to medium-sized neoplastic cells infiltration. Phenotypic markers expressed in ENKL include cytoplasmic CD3ε, CD56, and cytotoxic markers (granzyme B, perforin, TIA-1), but negative for surface CD3 (sCD3), CD5, or TCR (7,8). Epstein-Barr virus (EBV) can be sensitively detected in almost all of the ENKL patients by *in situ* hybridization (ISH) staining for EBV-encoded small nuclear RNA (EBER)-1, suggesting that EBV plays an important role in lymphomagenesis (1). Although the outcomes ENKL patients were improved recently, there are still many unresolved questions.

How to define high-risk ENKL?

While the majority of cases with ENKL present with localized disease within the nasal cavity, 18% may present in "extranasal" sites with a predilection for the skin, GI tract, adrenal glands, spleen and testis (9). The majority of patients with extranasal ENKL present with B symptoms, advanced stage and evidence of hemophagocytosis with resultant cytopenias. Therefore, ENKL nasal disease had a better median OS compared with extranasal presentation (9,10). Due to significant distinction in outcome between different localization of disease, accurate staging is needed. Positron emission tomography computed tomography (PET/CT), as a functional imaging technology, has exhibited high sensitivity for detection of occult disease (11,12). Compared with conventional staging methods, PET/CT demonstrated a significantly better sensitivity (97.7% *vs.* 80.7%, P=0.001) for the detection of malignant lesions (13).

The international prognostic index (IPI), originally designed for diffuse large B cell lymphoma (DLBCL), is the most common clinical prognostic model. The IPI score is of prognostic significance for ENKL (IPI <1 superior to IPI ≥2 for 20-year OS: 57.4% *vs.* 27.6%, P=0.012). However, the utility of IPI is limited because of the small sample size and heterogeneity of treatment regimen (14). A retrospective analysis of 262 patients revealed four prognostic factors: B symptoms, stage, lactate dehydrogenase (LDH) level, and regional lymph nodes. The new model (Korean international prognostic index, KIPI) showed a prognostic discrimination compared with IPI (15). However, this model is controversial, not validated in the International Peripheral T-cell Lymphoma Project (10).

Another prognostic marker for ENKL is the circulating plasma EBV-DNA, which is derived from apoptotic and necrotic cells (16,17). This is confirmed by a prospective study, which has shown the advantage of using plasma over peripheral blood mononuclear cell EBV-DNA (17). In another prospective study, plasma EBV-DNA of patients treated with SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) protocol was evaluated. Presentation of EBV-DNA was significantly associated with tumor load and treatment response. However, multivariate analysis indicated presentation EBV-DNA, IPI and KIPI were not independent prognostic factors. Therefore, EBV-DNA is just a marker of tumor load. On the other hand, negative EBV-DNA after one cycle of SMILE correlated with lower tumor load and superior survival. Furthermore, persistently undetectable EBV-DNA in patients achieving CR indicated superior outcome. These results indicate that a single measurement of EBV-DNA is not appropriate; it should be dynamically monitored (18).

Interim PET/CT has been found promising in predicting response and outcome of DLBCL and Hodgkin's lymphoma. The role of interim PET/CT in ENKL is yet undefined. In a prospective study, ENKL patients were treated with SMILE protocol, had PET/CT on diagnosis, mid-treatment (after 2-3 cycles of SMILE), end of treatment. Multivariate analysis showed Deauville score (DS) is the only significant independent predictor of both OS (P=0.004 and 0.018, respectively) and PFS (P=0.004 and 0.014, respectively). The estimated 2-year OS and PFS were 81% and 62%, respectively, in patients with a DS of 1-3, as compared with 17% in patients with a DS of 4-5 (P=0.001 and 0.001, respectively) (19). Therefore, interim PET/CT may play an important role in predicting survival of ENKL patients.

Which regimen is the best for newly diagnosed patients?

Due to the inspiring results of L-asparaginase in the treatment of relapsed/refractory ENKL, L-asparaginase-based regimen was explored for newly diagnosed ENKL. We conducted a prospective phase II study of L-asparaginase-based regimen in combination with radiotherapy. Thirty-eight ENKL patients were treated with CHOP-L (Cyclophosphamide, adriamycin, vincristine, prednisone, L-asparaginase). Thirty-one localized stage ENKL received radiation after 4-6 cycles of treatment. The median radiation dosage was 52 Gy, only two patients dosage was less than 50 Gy. The 2-year OS, PFS and DFS were 80.1%, 81% and 93.6%, respectively. Grade 3-4 leukopenia and neutropenia were 76.3% and 84.2%, respectively (6). NK/T-cell lymphoma cells express high levels of P-glycoprotein, which confers a multidrug resistance (MDR) phenotype (20). This is a major cause of the refractoriness of malignant lymphoma to conventional chemotherapeutic regimens containing anthracycline. Therefore, we replaced anthracycline with etoposide in the regimen CHOP-L, which is COEP-L, as the frontline regimen in newly diagnosed ENKL.

In a prospective study, 29 patients with newly diagnosed ENKL were treated with SMILE. A total of 19 patients received sandwiched involved-field radiotherapy, with a median dose of 50 Gy (30-52 Gy), the ORR was 90%, with CR rates 69%. Furthermore, 90% of patients remained in CR during follow-up. Grade 3/4 neutropenia occurred in 61% of patients. Regimen-related mortality was 7% (21).

Although the protocol SMILE achieved very promising results, the toxicities are nearly unacceptable. In a prospective study, twenty-seven newly diagnosed IE/IIE ENKL patients were treated with GELOX (gemcitabine, oxaliplatine, L-asparaginase) and sandwiched IFRT after at least two cycles of treatment. ORR was 96.3%, with CR achieved in 74.1%. With a median follow-up of 27 months, 2-year OS and PFS were both 86%. Grade 3-4 leukopenia was 33.3%, grade 3-4 thrombocytopenia was 29.6% (22). These results still require further investigation in larger prospective study.

What can we do for relapsed/refractory ENKL?

ENKL is a radiosensitive disease. Many studies indicate a dose-dependent survival benefit, with at least 50 Gy radiation dose (23-26). The largest series with radiotherapy

as a single modality treatment included 143 localized stage ENKL patients. A total of 104 patients received upfront involved-field radiation with a median dose of 50.4 Gy (range: 20-70 Gy), 69% of whom achieved a CR (27). Other studies have reported the similar results with CR rates between 52-100% (23-26). However, 25-40% patients underwent systemic relapse, suggesting single radiation modality is not enough for this group of patients.

L-asparaginase inhibits tumor cell growth *in vitro* by amino acid deprivation and subsequent inhibition of between protein, DNA and RNA synthesis. NK cells express low levels of asparagine synthase, and are therefore highly sensitive to L-asparaginase. Yong *et al*. first attempted to use L-asparaginase in refractory or relapsed ENKL in 1990 in our center (28-31). Eighteen patients with ENKL, who were refractory to CHOP-like regimen, received an L-asparaginase-based salvage regimen (L-asparaginase, vincristine, and dexamethasone). CR was 55.6%, with 5-year OS achieved in 55.6%. These results indicated that the L-asparaginase-based salvage regimen significantly improved the response rate and 5-year survival rate (30). Subsequently, another two studies from our center confirmed the remarkable efficacy of L-asparaginase in refractory/relapsed ENKL (5,31).

Based on these results, L-asparaginase has been incorporated into several regimens for relapsed/refractory ENKL. The most intense protocol is the regimen SMILE. In a prospective study that included 44 relapsed/refractory ENKL patients treated with SMILE regimen. The ORR was 77%, with CR achieved in 66%. The estimated 5-year OS was 52.3%; the 4-year disease-free survival was 68.2%. However, 72.7% of patients developed grade 3/4 neutropenia, and 42% with grade 3/4 thrombocytopenia; treatment related mortality was 7% (21). The French GELA and GOELAMS groups developed another L-asparaginase-containing regimen, AspaMetDex (L-asparaginase, methotrexate, and dexamethasone), which was evaluated in a multicenter phase 2 study. Nineteen relapsed/refractory ENKL patients were treated with 3 cycles of AspaMetDex. The ORR was 78%, with CR achieved in 61%. One-year OS was 47%. A total of 42% of patients developed grade 3/4 neutropenia (32). These data indicate that relapsed/refractory ENKL should be treated with L-asparaginase-containing regimens.

Currently, most patients receive L-asparaginase-based therapy as first-line treatment regimen. It is challenging to treat patients' refractory to or relapsed from L-asparaginase-based therapy. The efficacy of gemcitabine-based regimen has been evaluated retrospectively in 20 patients with relapsed/refractory ENKL. Fourteen patients had previously been treated with Lasparaginase-based chemotherapy. The ORR was 40% (CR =20%). The median PFS and OS were 2.3 and 4.9 months, respectively. For those who achieved CR or PR, the PFS was 7.3 months and the OS had not been reached (33). Therefore, gemcitabine-based regimens have shown activity in patients who are refractory to L-asparaginase-based chemotherapy.

The role of hematopoietic cell transplantation (HSCT) in ENKL

Autologous and allogeneic HSCT have been evaluated in newly-diagnosed and relapsed/refractory ENKL patients.

Given the inspiring results of combined chemotherapy and radiotherapy in early-stage ENKL, upfront autologous HSCT is not recommended in these patients. In a retrospective study, 16 ENKL patients were enrolled, including advanced-stage and high-risk patients. Nine patients received auto-HSCT in the first (CR1) or second complete remission (CR2). Seven patients received HSCT as salvage treatment. Estimated 2-year OS and relapse free survival were 71.3% and 25.8%, which showed a tendency of better survival compared with historical results (34). The role of HSCT is still unknown in the era of L-asparaginase-based treatment. In a prospective study of patients with relapsed/refractory ENKL disease salvaged with SMILE, 41% of patients remained in remission after SMILE alone, compared with 28% in those who received auto-HSCT (21). Therefore, the benefit of HCT was not apparent.

Allogeneic HSCT has been considered as curative treatment modality due to the graft-versus-lymphoma effect. However, there has been no prospective study to prove its benefit. A recent study examined the role of allogeneic HSCT in 18 patients, 14 of whom received SMILE prior to transplantation. With a median follow-up of 20.5 months, the estimated 5-year EFS and OS were 51% and 57% respectively. Grade 3/4 acute GVHD was observed in 11% of patients. The TRM was 22% (35). These results should be evaluated in prospective clinical trials.

New drugs and new methods

Histone deacetylases (HDACs) are a group of enzymes that play a major role in the epigenetic regulation of gene expression through their effects on the compact chromatin structure. In recent years, HDACs have become promising

therapeutic targets for T cell lymphoma. Treatment with romidepsin and belinostat lead to responses in patients with relapsed/refractory PTCL (36,37). These two HDAC inhibitors have been approved for PTCL by the US Food and Drug Administration (FDA). Brentuximab vedotin is an anti-CD30 antibody conjugate, which has been proved efficacious in CD30-positive lymphomas (38). CD30 is expressed in about 70% of ENKL (39). Lenalidomide is an immunomodulatory analog (IMiDs) with activity in lymphoid malignancies primarily through immune modulation. Lenalidomide has demonstrated efficacy in PTCL (40,41). Further studies are required to examine the effectiveness of these agents in ENKL.

Antigen-specific T cells targeting immunodominant viral antigens from EBV have been used with dramatic success to treat EBV-associated post-transplantation lymphoproliferative disease (PTLD) after bone marrow transplantation (42,43). EBV plays an important role in lymphomagenesis of ENKL. Patients with ENKL are associated with type II EBV latency, where only restricted, weakly immunogenic EBV antigens [latent membrane protein 1 (LMP1), LMP2, and EBNA1] are expressed (44). Of six ENKL patients treated with LMP-CTLs, four had complete responses, which remained in remission at a median of 3.1 years after CTL infusion (45). This study indicates autologous T cells directed to the LMP antigen can induce durable complete responses without significant toxicity.

Future directions

Recently, treatment outcome of ENKL has been improved remarkably. There are still many unresolved issues. In the future, we should identify better prognostic factors, improve chemotherapy regimens in newly-diagnosed and relapsed/refractory disease, and define the role of HSCT. The application of new drugs and new approach may improve the outcome of ENKL, but this needs further investigations.

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