Extranodal NK/T Cell Lymphoma, Nasal Type

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1 Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKL) is a distinct lymphoma characterized by predominant occurrence in nasal/paranasal area, skin/soft tissue, or gastrointestinal tract [1, 2]. The clinical course is aggressive, notably for disseminated cases, and used to result in poor prognosis [3–6]. Tumor cells of ENKL express multidrug resistance (MDR)-associated P-glycoprotein which actively export several cytotoxic agents such as doxorubicin, vincristine, or etoposide [7, 8]. This resulted in the poor response to conventional chemotherapy of lymphoma, mostly including anthracyclines [3–6]. After the extensive recognition of this lymphoma all over the world, the treatment paradigm has changed to simultaneous chemoradiotherapy for limited disease [9, 10] and L-asparaginase-containing chemotherapy for extensive disease [11, 12]. Currently, the prognosis of ENKL has been improved to be categorized in intermediate group and even better than that of mature T-cell lymphomas [2]. In this chapter, the particular features of this lymphoma are described.

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2 Epidemiology of NK/T-Cell Lymphoma

ENKL is an uncommon form of lymphoma which is much more prevalent in East Asia and Latin America. The incidence among all types of lymphoma is also different within the endemic areas; in East Asia, the rate of occurrence was 3 % in Japan [13] and in Malaysia [14], 4 % in Thailand [15], 6 % in Taiwan [16] and in Hong Kong [17], 9 % in Korea [18], and 11 % in China [19] (Fig. 1). In Western countries, although the subjected numbers are small, the incidence of ENKL was 2 % in France (4 of 192 patients), but 0 % in other countries [20]. Other anecdotal reports suggest that the rate ranges from 0 to 1 % in India, Australia, Greece, or Canada [21–24]. Although systematic incidence of lymphoma subtypes has not been reported from countries in Latin America, several studies suggest that considerable numbers of patients with ENKL do exist in Mexico, Peru, Brazil, and Singapore [25–28].

3 Pathology and Phenotype

Histologically, lymphoma cells of ENKL show diffuse proliferation with angiocentric or angiodestructive growth pattern (Fig. 2a). The cytological spectrum is rather broad, and cell sizes range from small to large. Varying degree of infiltration of inflammatory cells is presented and sometimes accompanies necrotic changes. These conditions caused the misunderstanding of this tumor as a nonneoplastic

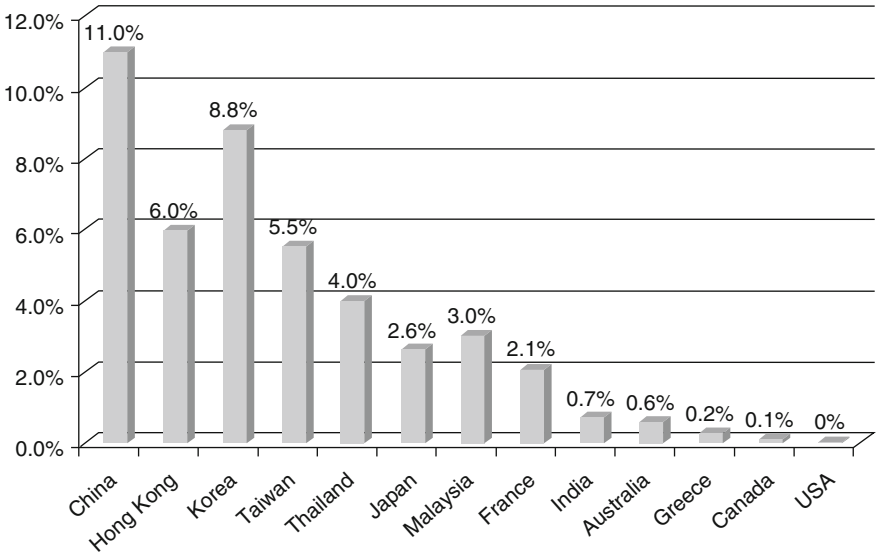

Fig. 1 Ratio of ENKL in malignant lymphoma among each country

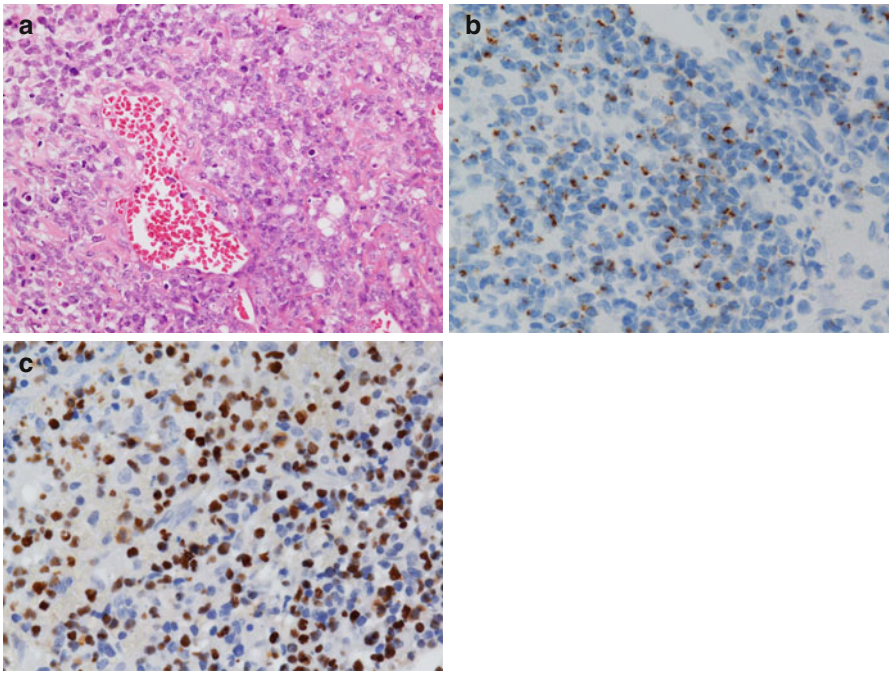

Fig. 2 Histologic features of ENKL. Tumor cells show an angiocentric growth pattern with infiltrating inflammatory cells and necrosis (**a**). The neoplastic cells are positive for granzyme B (**b**) and Epstein-Barr virus, detected by EBER in situ hybridization (**c**)

condition, particularly for nasal lymphomas [1, 29]. Repeated biopsies are important for precise diagnosis of those cases. Uncommon case of ENKL with intravenous lymphoma is recognized occasionally (Fig. 3) [30]. This suggests that intravascular form of lymphoma is not B-cell specific.

The lymphoma cells express NK-cell markers that include CD2, cytoplasmic CD3 (cyCD3), CD7, and CD56. Surface CD3 (sCD3), CD5, and T-cell receptor (TCR) are generally negative, and TCR genes show germline configurations. Cytotoxic molecules such as TIA-1, granzyme B, and perforin are also positive in this lymphoma (Fig. 2b). Lymphoma cells are also positive for Epstein-Barr virus (EBV), which is currently regarded as a hallmark of ENKLs [30]. The EBV in specimens can be detected by EBER in situ hybridization (Fig. 2c).

4 Clinical Presentation

ENKL mostly occurs in adults with median age of 40s to 50s and shows remarkable male predominance [3–6, 25–28, 31–34]. Upper aerodigestive tract, typically nose or paranasal area, is the most affected site of origin, followed by the skin and

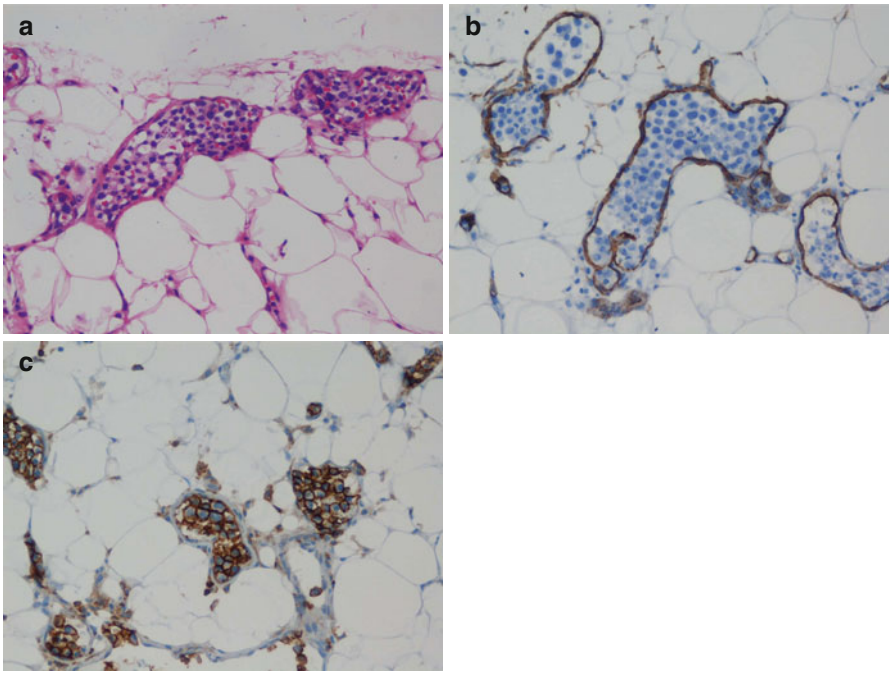

Fig. 3 ENKL of intravascular lymphoma. A rare form of ENKL presents with intravascular lymphoma (**a**). The CD34 staining highlights the localization of lymphoma cells in the vessels (**b**). Lymphoma cells are positive for CD56 (**c**)

gastrointestinal tract. For ENKL with nasal origin, approximately half of the patients present with stage I disease and one fourth with stage II [3, 5, 26–28, 32]. Some patients show long-term limitation to the original site, mimicking chronic sinusitis. On the other hand, extensive-stage disease can rapidly progress with fever, bone marrow involvement, hemophagocytosis, and disseminated intravascular coagulation. In contrast to nasal cases, two thirds of extra-nasal ENKLs present with advanced stage [5, 6]. In the 4th WHO classification, both nasal and extra-nasal ENKLs are included in the same category of disease [1] but should separately be assessed for clinical management.

5 Differential Diagnosis

For precise diagnosis of ENKL, several NK-cell-associated diseases should differentially be diagnosed. Those include aggressive NK-cell leukemia (ANKL), lymphomatoid gastroenteropathy (LyGa), and chronic NK-cell lymphocytosis (CNKL).

5.1 Aggressive NK-Cell Leukemia

ANKL is a leukemic form of NK-cell malignancy and accounts for less than 1 % of the lymphoid malignancies [13, 19]. It predominantly occurs in younger patients than ENKL with a median age around 40 years without any sex predominance [35]. The disease progression is rapid, and patients frequently present with B symptoms, such as fever, night sweat, or body weight loss. Hematological manifestation of ANKL is that of leukemia, which includes circulating and bone marrow leukemic cells, neutropenia, anemia, and thrombocytopenia, but hepatosplenomegaly is also frequently recognized. Cutaneous or central nervous system involvement is uncommon. Leukemic cells present as large granular lymphocytes and express NK-cell antigens including CD2+, cytoplasmic CD3, CD7, CD16, and CD56. EBV is usually positive, but not exclusively [35, 36]. Expression of CD16 is more frequent in ANKL than in ENKL, reflecting the different maturation stage of NK-cells: the former from cytotoxic NK-cells and the latter from immunoregulatory NK-cells [37]. The genetic differences of ANKL and ENKL including genomic gain and loss were revealed by array-based comparative genomic hybridization [38]. Anthracycline-based chemotherapy showed only limited response, but efficacy of L-asparaginase has recently been documented. Dose-reduced SMILE or L-asparaginase mono-induction is recommended for treatment [39].

5.2 Lymphomatoid Gastroenteropathy

The LyGa or NK-cell enteropathy is characterized by a localized proliferation of NK-cells, mostly in the stomach, but less frequently in the intestine [40, 41]. Patients do not show specific symptoms, and most are found by chance through endoscopic examination or follow-up of gastric cancer. Macroscopic findings show protruded lesion(s) in the stomach with around 1 cm diameter with or without depression or ulcers. Histologic specimens show sheeted proliferation of NK-cells without any accompanying necrotic areas. EBV is negative and can be a hallmark of differential diagnosis from ENKL. Lymphoepithelial lesions are occasionally found, and eosinophilic granules are seen in proliferating NK-cells. *Helicobacter pylori* infection is often accompanied, but its significance remains uncertain. The lesions usually disappear without any medications, and the recurrences are rare. The most important point for this disease is to avoid chemotherapy for lymphoma.

5.3 Chronic NK-Cell Lymphocytosis

CNKL is characterized by a chronic increase of blood NK-cells without lymphadenopathy or organomegaly [42]. The term “lymphocytosis” is derived from its non-neoplastic nature without any cytogenetic abnormalities. However, peripheral blood

counts and morphology of increased NK-cells resemble those of ANKL. EBV is usually undetectable in CNKL; hence, the examination of EBV may help the differential diagnosis [43]. Rare cases of CNKL were reported to develop to ANKL [44], but these may represent occult ANKLs in the category of CNKL rather than transformation. CNKL is sometimes associated with reactive conditions against viral infections or underlying solid tumors [42]. Examinations of whole body and watchful observations are thus recommended as managements of CNKL.

6 Treatment of ENKL

6.1 Limited Stages

Radiotherapy has been the mainstay for the treatment of ENKL with limited stage disease. Since anthracyclines and vincristine are exported from lymphoma cells of ENKL by p-glycoprotein [7, 8], the efficacy of CHOP/CHOP-like regimen was unsatisfactory [5, 45]. Radiotherapy should be given prior to [46] or simultaneous with chemotherapy [9, 10]. The chemotherapy to be combined with radiotherapy is not determined, but platinum-based regimens are preferentially used. The Japanese Clinical Oncology group conducted a phase II study of simultaneous chemoradiotherapy (SCRT) with 50 Gy irradiation and the 2/3 dose of DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) (Table 1) [9]. Two thirds of DeVIC was repeated 3 cycles, and the total treatment period was 9 weeks. The study by Korean group adopted a cisplatin monotherapy for SCRT followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) regimen [10]. Both studies showed satisfactory results with 2-year OS of approximately 80 % (Table 2), and the long-term follow-up study of RT-2/3 DeVIC confirmed the durable efficacy with 5-year OS of 70 % [47].

6.2 Advanced Stages, Relapsed or Refractory State

Systemic chemotherapy is required for advanced stage, relapsed or refractory ENKL patients. However, the efficacy of CHOP/CHOP-like regimen is limited because of the expression of p-glycoprotein [5]. Based on the clinical experience and in vitro

Table 1 RT-2/3 DeVIC regimen

Agent	Dose	Administration	Days
Radiotherapy	1.8–2.0 Gy	(Total 50 Gy)	Days 1–33 or 38 (5–6 weeks)
Carboplatin	200 mg/m^2	30 min div	Day 1 (22, 43)
Etoposide	67 mg/m^2	2 h div	Days 1–3 (22–24, 43–45)
Ifosfamide	1000 mg/m^2	3 h div	Days 1–3 (22–24, 43–45)
Dexamethasone	40 mg/body	30 min div	Days 1–3 (22–24, 43–45)

2/3 DeVIC should be repeated every 3 weeks

Table 2 Comparison of simultaneous chemoradiotherapy (SCRT) for localized ENKL

Regimen	RT-2/3 DeVIC	Korean CCRT
Treatment period	9 weeks	16–20 weeks
Radiation dose	50 Gy	40–50.8 Gy (median: 40 Gy)
Cytotoxic agents	CBDCA	CDDP
	ETP	ETP
	IFM	IFM
	Dexa	Dexa
Chemotherapy	3 courses	SCRT + 3 courses
Number of patients	27	30
Stage I ratio	67 %	50 %
CR rate	77 %	73 % → 90 % (best response)
ORR	81 %	100 %
2y OS	78 %	86 %
95 % CI	(57–89 %)	(74–99 %)
Median f/u	32 months	23.7 months
Range	(24–62 months)	(17.3–37 months)
5y OS	70 %	–
95 % CI	(49–84 %)	–
Median f/u	67 months	–
Range	(61–94 months)	–

Abbreviations: *JCOG* Japan Clinical Oncology Group, *CCRT* concurrent chemoradiotherapy, *CBDCA* carboplatin, *ETP* etoposide, *IFM* ifosfamide, *Dexa* dexamethasone, *CDDP* cisplatin, *CR* complete response, *ORR* overall response rate, *OS* overall survival, *CI* confidence interval, *f/u* follow-up

Table 3 SMILE regimen

Agent	Dose	Administration	Days
Methotrexate	2 g/m^2	6 h div	Day 1
Ifosfamide	1500 mg/m^2	3 h div	Days 2–4
Etoposide	100 mg/m^2	2 h div	Days 2–4
Dexamethasone	40 mg/body	30 min div	Days 2–4
L-asparaginase	6000 IU/m^2	2 h div	Days 8, 10, 12, 14, 16, 18, 20

SMILE should be repeated every 4 weeks

sensitivity studies, L-asparaginase-containing regimens have been established and became the first choice for these patients [48]. L-asparaginase is an enzyme that digests serum L-asparagine and acts as an antitumor agent through asparagine starvation of tumors with low expression levels of asparagine synthetase [49]. The SMILE regimen consists of steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (Table 3) [50]. The phase II SMILE study showed an excellent antitumor activity to ENKL (Fig. 4) [11], and the efficacy was further verified by a long-term follow-up with a 3-year OS of 50 % (95 % CI, 33–65 %) [51]. Another L-asparaginase-containing regimen, AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) was studied by GELA (Groupe d'Etude des Lymphomes de l'Adulte) and GOELAMS (Groupe Ouest-Est des Leuce'mies et des Autres Maladies du Sang) [52].

Table 4 Comparison of L-asparaginase-containing regimens for ENKL

Regimen	SMILE	AspaMetDex
Agents	MTX	MTX
	L-asp	L-asp
	Dexa	Dexa
	ETP	
	IFM	
Number of patients	38	19
Course	2 courses	3 courses
Chemotherapy interval	4 weeks	3 weeks
Rate of stage III/IV patients	71 %	37 %
CR rate	45 %	61 % (1 patient excluded)
ORR	79 %	78 %
2y OS	51 %	41 %
Median f/u	24 months	26 months
Range	(13–35 months)	(17–49 months)
In case of L-asp allergy	SMILE head is strong enough	MTX monotherapy

Abbreviations: *NKTSG* NK-cell Tumor Study Group, *MTX* methotrexate, *L-asp* L-asparaginase, *Dexa* dexamethasone, *ETP* etoposide, *IFM* ifosfamide, *CR* complete response, *ORR* overall response rate, *OS* overall survival, *f/u* follow-up

The phase II study of AspaMetDex for relapsed or refractory ENKL also showed a good overall response rate and 1-year OS [12]. However, results of a later-conducted study for newly diagnosed ENKL patients were rather unsatisfactory [53]. Although more than half of the patients were in localized stage, the ORR was 55 % (95 % CI, 32–77 %) and OS was less than 50 %. All patients examined developed an anti-asparaginase antibody, partly due to the low-intensity chemotherapy before L-asparaginase. The comparison of these two L-asparaginase-based chemotherapy is shown in Table 4. SMILE is sometimes myelotoxic to ENKL patients, but the duration of neutropenia is generally not so long (Fig. 5). It is therefore needed to identify patients who develop severe leukopenia and neutropenia after SMILE regimen.

6.3 Hematopoietic Stem Cell Transplantation

Previously, prognosis of ENKL was recognized as poor even for limited stage patients. Therefore, both autologous and allogeneic hematopoietic stem cell transplantations (HSCTs) were conducted for ENKL with every situation [54]. A long-term survival for ENKL patients who received upfront autologous HSCT ranged from 50 to 70 % [54–56]. The matched-control study comparing autologous HSCT and conventional radiochemotherapy showed that the advantage of autologous HSCT was evident only for patients with high-risk prognostic index [57]. Allogeneic HSCT showed a long-term survival rate ranging from 30 to 40 % [54, 58], but the patient background characters were worth than those of autologous HSCT. Patients who received allogeneic

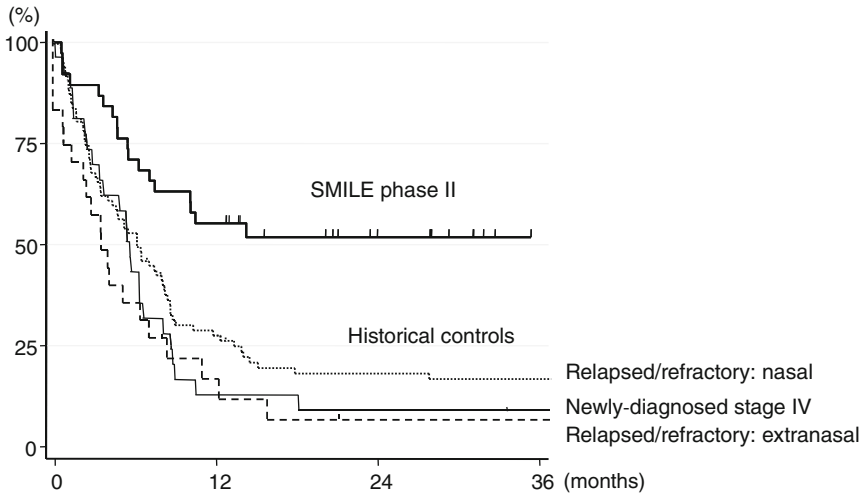

Fig. 4 Survival of newly diagnosed stage IV or relapsed/refractory ENKL. The survival curve of SMILE phase II study is overlaid on those of historical control and is markedly improved. However, these curves are not exactly comparable because of background differences

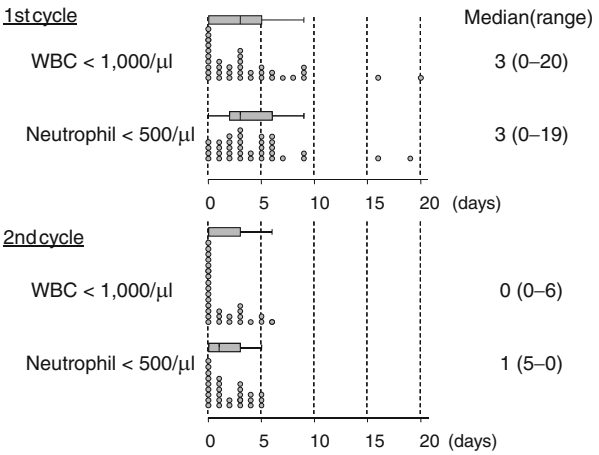

Fig. 5 Duration of cytopenia after SMILE. Although several patients developed prolonged leukocytopenia and neutropenia, the durations of cytopenia were generally not so long. Both the median of leukocyte less than 1,000/μl and that of neutropenia less than 500/μl were 3 days. The durations of cytopenia were rather short after the second course of SMILE as compared with the first course

HSCT were more likely to be in non-CR condition and to have higher clinical stage at diagnosis, although the age was lower. No superiority of either autologous or allogeneic HSCT has been identified, as well as the conditioning intensity of reduced vs. myeloablative conditioning [59, 60]. In the current decade, the treatment modality was changed and prognosis was improved by an introduction of SCRT and L-asparaginase-containing chemotherapy; hence, new questions are raised for the significance and methodology of HSCT for ENKL. Further investigations and prospective evaluations are needed to clarify the indication of HSCT for NK/T-cell lymphoma.

7 EBV-DNA in Peripheral Blood

In the process of tumor growth, cell-free DNA fragments are released from apoptotic/necrotic tumor cells to circulating peripheral blood. For patients with ENKL, the EBV-DNA can be detected as a part of tumor DNA [61]. These viral DNA fragments are usually less than 500 bp in length and can be detected by polymerase chain reaction [62]. Measurement of the circulating EBV-DNA copy numbers is useful for diagnosis, monitoring, and prognostication of the disease [63–65]. There are several choices of source tissue for analysis including mononuclear cells, plasma, and whole blood, and each choice represents a different outcome [64]. The SMILE-EBV study further identified that the amount of EBV-DNA predicted the degree of adverse reactions by SMILE chemotherapy [66]. One reason for this phenomenon is that the toxicity by chemotherapy is mediated by certain toxic substances released from tumor cells, such as cytotoxic molecules. This is also important for patient case, since the initial dose of chemotherapy for patients with high tumor burden may be decreased to avoid excessive toxicity.

8 Prognostic Factors for ENKL

The International Prognostic Index (IPI) score is a good indicator for prognosis of ENKL [3–6], like most of other types of lymphoma. However, among the components of IPI, the age is not prognostic in many observations [4, 5]. Other adverse prognostic factors specific for ENKL are the non-nasal origin of lymphoma [5, 6], local tumor invasiveness [67], and the regional lymph node involvement [4]. Poor prognosis of the non-nasal origin is partly due to the difference in stage distribution [68], but is still prognostic after adjustment by multivariate analysis [5]. This warrants future division of disease subtypes of nasal and non-nasal ENKLs in the lymphoma classification. The local tumor invasiveness included bony invasion or perforation or invasion of the skin based on computed tomography or physical findings [67]. However, these extreme local progressions are currently rare due to the early disease recognition and reference to specialized physicians. The regional lymph node involvement was defined as the involvement of lymph nodes corresponding to N1, N2, or N3, but not M1 of the TNM staging system [4]. The incidence of regional lymph node swelling ranges from 30 to 50 %.

9 Future Perspectives

Several new insights have been developed for ENKL. The disease is currently recognized to belong to intermediate prognosis [2]. Further improvement for diagnosis and treatment should be explored by prospective clinical studies.

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