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Current status and progress of lymphoma research in East Asian countries

Novel findings from the Asian Lymphoma Study Group: focus on T and NK-cell lymphomas

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Abstract

T and NK-cell lymphomas are aggressive neoplasms with a unique epidemiological distribution, demonstrating higher prevalence in Asian countries compared to the West. Through the efforts of international collaboration, significant progress has been made especially on the biological understanding and clinical management of rare lymphoma subtypes including NK/T-cell lymphomas and monomorphic epitheliotropic intestinal T-cell lymphoma. In this review, we summarize the current status of lymphoma research conducted by the Asian Lymphoma Study Group and highlight key updates on the advancement of T and NK-cell lymphoma research.

Keywords JAK-STAT pathway · NK/T-cell lymphoma · Enteropathy-associated T-cell lymphoma · Epstein–Barr virus

Abbreviations

NKTCL	NK/T-cell lymphoma
MEITL	Monomorphic epitheliotropic intestinal T-cell lymphoma
ALSG	Asian Lymphoma Study Group
ICGC	International Cancer Genomic Consortium

Introduction

The epidemiology of non-Hodgkin lymphoma exhibits a unique geographic diversity, with a high prevalence of T-cell and NK/T-cell lymphomas in Asian countries compared to the West [1, 2]. Over the past decade, significant progress has been made in the clinical management of non-Hodgkin lymphoma in Asia. On the research front, the Asian Lymphoma Study Group (ALSG) brings together centers across East Asia to collaborate on studies on Asia-centric lymphoma, with participating members from Japan, South Korea, China, Taiwan, Singapore, Malaysia, Indonesia and Thailand. To date, the ALSG has published several important research findings across different lymphoma subtypes, including landmark discoveries on NK/T-cell lymphomas (NKTCL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) (Tables 1, 2). In addition, the Singapore Lymphoma Study Group has been leading the whole genome sequencing of T and NK-cell lymphomas in the International Cancer Genomic Consortium (ICGC), illuminating major pathways and fundamental biological mechanisms underlying these diseases. In this review, we summarize the current status of lymphoma studies conducted by the ALSG and highlight key updates on the progress of T and NK-cell lymphoma research.

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Extranodal NK/T-cell lymphoma

Introduction and clinical features

NKTCL is an aggressive Epstein–Barr virus (EBV)-associated hematological malignancy, with a predilection for extranodal involvement. Over the past years, the ALSG has taken a keen interest in understanding the molecular and clinical pathobiology of NKTCL. Epidemiologically,

Table 1 Key publications on NKTCL from Asia (2009–2017)

Year of publication	Study highlights	References
Consensus guidelines and selected clinical series		
2009	First multicentre consensus statement and resource-stratified guidelines on the optimal approach to diagnosis, staging, follow-up, and treatment of T and NK-cell neoplasms in Asia	[1]
2013	Retrospective series of patients with gastrointestinal NKTCL demonstrating poor median overall survival of 7.8 months despite active management with chemotherapy and surgery	[4]
2015	Retrospective series of patients with primary cutaneous nasal-type NKTCL and EBV-negative CD56-positive PTCL from Asia demonstrating poor 5-year overall survival rates of 25%	[5]
Treatment developments in localized NKTCL		
2009	Phase II study of concurrent chemoradiation using weekly cisplatin followed by VIPD (etoposide, ifosfamide, cisplatin, dexamethasone) in newly diagnosed localized NKTCL achieved a complete response rate of 80% and 3-year overall survival of 86%	[10]
2012	Phase II study of concurrent chemoradiation using the DeVIC regimen (dexamethasone, etoposide, ifosfamide, carboplatin) in newly diagnosed localized NKTCL reported a complete response rate of 77% and 5-year overall survival of 70%	[9]
2017	Retrospective analysis on patients with localized NKTCL demonstrating comparable outcomes with either concurrent or sequential chemoradiation, achieving a 5-year overall survival of over 70%	[13]
Treatment developments in advanced NKTCL		
2011	Initial phase II study on the SMILE regimen on patients with newly diagnosed or relapsed/refractory NKTCL, reporting an overall response rate of 79% after 2 cycles, with an updated 5-year overall survival of 47%	[11]
2012	Prospective confirmatory study of the SMILE regimen on patients with newly diagnosed and relapsed/refractory NKTCL, reporting an overall response rate of 81% and 5-year overall survival of 50%	[12]
2014	Retrospective series showing that allogeneic transplant in NKTCL achieved a 5-year overall survival of 57% and 5-year event-free survival of 51%, and that the use of the SMILE regimen pre-transplant was the most important prognostic indicator of superior survival outcomes	[17]
2015	Retrospective series demonstrating that upfront autologous transplant achieved a 3-year overall survival of 60% and 3-year progression-free survival of 52%, and is a feasible and effective therapy in NKTCL patients who respond to initial primary therapy	[18]
2017	Seven male patients with NKTCL who had failed L-asparaginase regimens and/or allogeneic transplant achieved treatment response to pembrolizumab according to various assessment criteria, with 5 patients achieving complete remission	[19]
Prognostic models		
2015	Post-treatment circulating EBV DNA and PET–CT scoring independently associated with progression-free and overall survival after completion of primary treatment for NKTCL	[30]
2016	Prognostic Index of Natural Killer lymphoma (PINK) model derived from a retrospective study of patients who had received non-anthracycline-based treatment. Four risk factors—age greater than 60 years, stage III or IV disease, distant lymph node involvement and non-nasal type strongly associated with poor survival outcomes	[28]
Molecular pathogenesis		
2012	Whole exome sequencing identified *JAK3* somatic mutations in 35% of NKTCL cases, leading to constitutive activation of JAK-STAT signaling and increased cell growth	[34]
2015	Whole exome sequencing identified recurrent somatic mutations in the RNA helicase gene *DDX3X* in 20% of NKTCL cases, as well as tumor suppressors (*TP53* and *MGA*), JAK-STAT-pathway molecules (*STAT3* and *STAT5B*) and epigenetic modifiers (*MLL2*, *ARID1A*, *EP300* and *ASXL3*)	[33]

Table 1 (continued)

Year of publication	Study highlights	References
2016	Genome-wide association study identified strong associations between *HLA-DPB1* single-nucleotide polymorphisms and susceptibility to NKTCL	[32]

NKTCL NK/T cell lymphoma, *PTCL* peripheral T-cell lymphoma

Table 2 Key publications on MEITL and other PTCL from Asia

Year of publication	Study highlights	References
MEITL		
2011	Clinicopathological characterization of MEITL demonstrating frequent γδ T-cell receptor expression and the consistent presence of intraepithelial lymphocytosis	[38]
2011	Extensive nuclear expression of megakaryocyte-associated tyrosine kinase (MATK) and a CD8(+)CD56(+) cytotoxic phenotype characterizes MEITL, distinguishing it from classical type I EATL	[39]
2012	Retrospective series on patients with MEITL demonstrating that the most common site of involvement (> 80%) was the small bowel, and that median overall survival was a dismal 7 months	[37]
2013	Molecular pathological study demonstrating that the majority of neoplastic cells in MEITL express CD8αα homodimers, and may reflect tumor progression from intraepithelial T-cell precursors	[40]
2016	Next generation sequencing identified prominent activation of JAK-STAT and G-protein coupled receptor signaling pathways in MEITL. Mutations in *STAT5B*, *JAK3* and *GNAI2* were detected, with the majority occurring at known activating hotspots in key functional domains	[41]
PTCL		
2014	Gene expression profiling identified unique signatures for major histological subgroups of PTCL, including angioimmunoblastic T-cell lymphoma, anaplastic lymphoma kinase (ALK)-positive and ALK-negative anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma and NKTCL	[42]
2017	Gene expression profiling showed that compared with extranodal NKTCL, EBV-positive variant of PTCL, non-otherwise specified ("primary nodal NKTCL") was distinctively characterized by upregulation of PD-L1 and T-cell related genes, downregulation of CD56, as well as loss of 14q11.2 which correlated with loss of TCR loci and T-cell origin	[43]

MEITL monomorphic epitheliotropic intestinal T-cell lymphoma, *PTCL* peripheral T-cell lymphoma, *EATL* enteropathy-associated T-cell lymphoma, *EBV* Epstein–Barr virus

NKTCL demonstrates a geographic distribution that is more predominant in East Asia and South America compared to European and North American countries, with an incidence of around 3–10% and less than 1%, respectively. In most cases, NKTCL presents as a destructive lesion in the nasal cavity and upper aerodigestive tract, although involvement of non-nasal regions have been described [3]. Extranasal NKTCL are characterized by more adverse clinical features, with worse overall survival outcomes in both early and late stage disease, compared to nasal subtypes [3]. In a retrospective analysis of 81 patients with gastrointestinal NKTCL from the ALSG, the majority involve the small intestine and more than 60% present with advanced disease. Despite active management with chemotherapy and surgery, median overall survival remains a dismal 7.8 months [4]. Another retrospective clinicopathologic study describing 60 patients with primary cutaneous nasal-type NKTCL and CD56-positive EBV-negative peripheral T-cell lymphoma (PTCL) from Asia demonstrated equally poor outcomes with a 5-year overall survival rate of only 25% [5].

Clinical management updates

The standard management of NKTCL is steadily evolving and current recommendations have been excellently summarized in recent reviews [6, 7]. Traditional treatment with anthracycline-containing regimens has been largely ineffective due to tumor expression of P-glycoprotein, and current treatment strategies for nasal-type NKTCL include mainly chemoradiation for localized disease [8–10] and L-asparaginase-based systemic chemotherapy for advanced cases [11, 12]. In localized NKTCL, the optimal sequencing of radiotherapy and chemotherapy remains a controversy. A recent retrospective analysis of a multicentre patient cohort showed that both concurrent and sequential chemoradiation resulted in similar outcomes, achieving an overall survival of over 70% after 5 years [13]. For advanced NKTCL, the SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) chemotherapy regimen is frequently adopted in Asia. The initial phase II study on 38 newly diagnosed or relapsed/refractory NKTCL reported an overall response

rate of 79% after 2 cycles, with an updated 5-year overall survival of 47% [11, 14]. A subsequent study from the ALSG confirmed the efficacy outcomes, reporting an overall response rate of 81% and 5-year overall survival of 50% [12]. Despite these encouraging results compared to anthracycline-based regimens, the SMILE protocol is associated with unavoidable myelosuppression which can be severe despite G-CSF support, with grade 4 neutropenia occurring in most patients [11]. Supportive care strategies such as optimizing antibiotic prophylaxis and managing L-asparaginase hypersensitivity reactions have been proposed to minimize the occurrence of treatment-induced toxicities [15].

In the contemporary management of NKTCL using L-asparaginase-based regimens, the role of high-dose chemotherapy with hematopoietic stem cell transplant (HSCT) in NKTCL is highly controversial. In the pre-SMILE era, a retrospective multicentre analysis including ten patients with NKTCL undergoing autologous or allogeneic hematopoietic stem cell transplant reported dismal outcomes with 5-year overall survival of 38% and progression-free survival of 37%, with the lack of attaining complete or partial response at the time of transplant associated with worse outcome [16]. More recently, in a multicentre analysis of 18 patients from the ALSG, Tse and Kwong showed that allogeneic transplant achieved a 5-year overall survival of 57% and 5-year event-free survival of 51%, and that the use of the SMILE regimen pre-transplant was the most important prognostic indicator of superior survival outcomes. This study included patients with stage IV disease with bone marrow involvement at first complete remission or chemotherapy-sensitive relapsed/refractory disease. The majority of patients in this study received the SMILE regimen, and all except two patients were in complete remission at the time of transplant, probably accounting for the improved outcomes [17]. Similarly, upfront autologous HSCT has also been reported to be a feasible and effective therapy in NKTCL patients who respond to initial primary therapy [18]. Despite feasibility and efficacy data, given the comparable rates of efficacy outcomes achievable by SMILE or other L-asparaginase-based regimens alone, the exact utility of HSCT remains to be clarified in future studies.

Novel therapies

Salvage options post L-asparaginase regimens are currently lacking, though emerging data for novel therapeutic options are emerging. Recently, the ALSG reported remarkable response rates to the anti-programmed death 1 (PD1) antibody pembrolizumab in relapsed/refractory NKTCL. Seven male patients with NKTCL who had failed L-asparaginase regimens and/or allogeneic HSCT achieved treatment response according to various assessment criteria, with 5 patients achieving complete remission. Blockade of the PD1/PDL1 axis in NKTCL certainly deserves further investigation in future studies [19]. We previously reported a single patient with relapsed disease who achieved complete response to B-GIFOX (bortezomib, gemcitabine, ifosfamide and oxaliplatin) [20]. The activity of gemcitabine-containing therapies in relapsed/refractory NKTCL was similarly observed in a retrospective cohort of 20 patients, with an overall response rate of 40% [21]. Alisertib is an inhibitor of Aurora A kinase, a centrosome-associated serine/threonine kinase which is overexpressed or amplified in a range of hematologic and non-hematologic malignancies [22]. A phase I study conducted on East Asian patients investigated the safety and tolerability of twice daily alisertib for 7 days in a 3 weekly cycle. Among 36 patients, which included 3 patients with NKTCL, the best response was a partial response in a patient with nasal-type NKTCL, achieving a duration of response of 5.6 months while on the established maximum tolerated dose of 30 mg BID [23]. Other significant case reports in the setting of relapsed/refractory NKTCL include sustained responses to anti-CD30 therapy with brentuximab vedotin [24], and anti-CD38 antibody daratumumab [25].

Prognostication and risk stratification

Despite improved outcomes with the incorporation of L-asparaginase-based chemotherapy regimens as well as radiotherapy in the management of NKTCL, a substantial group of patients still experience treatment failure and disease relapse. Several prognostic models have been developed based on patients treated with anthracycline-based regimens [3, 26, 27], undermining their relevance in the present era. Recently, a Prognostic Index of Natural Killer lymphoma (PINK) model was derived from a retrospective study of patients who had received non-anthracycline-based treatment in the International NK/T-Cell Lymphoma Project [28]. Four risk factors—age greater than 60 years, stage III or IV disease, distant lymph node involvement and non-nasal type were strongly associated with worse survival outcomes. Patients in the highest risk group had a 3-year overall survival of less than 30%, highlighting profound inadequacies even with contemporary treatment approaches. Circulating EBV DNA in the peripheral blood has been correlated with tumor load, and has been associated with treatment response, toxicity, and survival in patients with NKTCL [29]. In corroboration with this result, the addition of detectable pre-treatment EBV DNA levels to the PINK model had similarly segregated patients into distinct prognostic groups [28]. The ALSG recently conducted a retrospective assessment of the prognostic relevance of post-treatment circulating EBV DNA as well as PET–CT scoring by the Deauville system, both of which were independently associated with progression-free and overall survival [30].

Molecular pathobiology

The molecular pathways implicated in the pathobiology of NKTCL are still poorly understood [31]. To understand the molecular epidemiology of this disease, we had previously conducted the first genome-wide association study on a large cohort of more than 500 patients with NKTCL. We identified strong associations between *HLA-DPB1* single-nucleotide polymorphisms and susceptibility to NKTCL, implicating altered antigen processing and presentation to CD4-positive T lymphocytes in the pathogenesis [32]. In recent years, next generation sequencing has led to a greater clarity of the genomic landscape of NKTCL, revealing recurrent somatic mutations such as *TP53*, *JAK3*, and *DDX3X* in NKTCL [33–35]. Using whole exome sequencing, we previously identified *JAK3* somatic mutations in 35% of NKTCL cases, leading to constitutive activation of JAK-STAT signaling and increased cell growth [34]. Similarly, another study by Lee et al. demonstrated frequent mutations (56%) of *STAT3* and other mutations in the JAK-STAT cascade in a cohort of 34 NKTCL tissue samples and cell lines. Interestingly, histone modification-related genes including *BCOR* and *MLL2* were mutated in 38% of the samples, supporting a role for epigenetic dysregulation in NKTCL [35]. Most recently, our group investigated the interaction between JAK-STAT pathway signaling and the PD-L1 immune checkpoint protein. Using targeted sequencing of 188 genes associated with the JAK-STAT pathway in 109 NKTCL samples, we characterized a novel E616K mutant residing in the SH2 domain of *STAT3*. E616K not only conferred IL-3 independent growth to Ba/F3 cells and increased STAT3 phosphorylation, PD-L1 was also found to be overexpressed. Though preliminary, this suggests that the oncogenic JAK-STAT signals may promote NKTCL development by driving immune evasion [36]. Consequently, the combined inhibition of the PD-1/PD-L1 axis and JAK-STAT pathway may be a promising therapeutic approach for NKTCL.

Monomorphic epitheliotropic intestinal T-cell lymphoma and other peripheral T-cell lymphoma

MEITL, previously known as type II enteropathy-associated T-cell lymphoma (EATL), is a rare and aggressive non-Hodgkin lymphoma arising from the intestinal tract. Whilst classical type I EATL is associated with celiac disease and is predominant in Western populations, type II EATL lacks this association and is more prevalent in Asia [37, 38]. Even so, a previous retrospective study by the ALSG identified only 38 patients in 4 institutions within a 19-year period. The most common site of involvement (> 80%) was the small bowel, and the presenting features were perforation, pain and obstruction. Median overall survival was a dismal 7 months [37]. Histologically, MEITL is characterized by central sheets of monotonous neoplastic lymphocytes, a peripheral zone infiltrated by atypical intraepithelial lymphocytes (IELs), and distant mucosa with normal villous architecture and morphologically normal IELs. Distinct from classical type I EATL, extensive nuclear expression of megakaryocyte-associated tyrosine kinase (MATK) and a CD8(+)CD56(+) cytotoxic phenotype typifies the diagnosis of MEITL [39]. The majority of neoplastic cells express CD8αα homodimers, and may reflect tumor progression from intraepithelial T-cell precursors [40]. Recently, we demonstrated that JAK-STAT and G-protein coupled receptor signaling pathways are prominently activated in MEITL [41]. Mutations in *STAT5B* (63%), *JAK3* (35%) and *GNAI2* (24%) were detected, with the majority occurring at known activating hotspots in key functional domains. Our in vitro data further suggested that targeted inhibition of these pathways may be useful in treatment of this disease.

In other PTCLs, gene expression profiling identified unique signatures for major histological subgroups, including angioimmunoblastic T-cell lymphoma (AITL), anaplastic lymphoma kinase (ALK)-positive and ALK-negative anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma and NKTCL [42]. This classification allowed the identification of novel diagnostic and prognostic subtypes of PTCL, and provided biological rationale for novel therapeutic targets in this heterogeneous group of diseases. In a more recent study, we examined primary nodal NK/T-cell lymphoma—a clinically ambiguous entity currently included in the revised 2016 WHO lymphoma classification as an EBV-positive variant of PTCL, not otherwise specified [43]. Compared with extranodal NKTCL, this nodal phenotype was distinctively characterized by upregulation of PD-L1 and T-cell-related genes, downregulation of CD56, as well as loss of 14q11.2 which correlated with loss of TCR loci and T-cell origin.

Conclusion and future perspectives

In recent years, we have witnessed encouraging progress in lymphoma research across East Asia. The ALSG has taken on a key leadership role in attempting to advance clinically relevant research particularly on the more Asian-centric lymphoma subtypes such as NKTCL and MEITL. Nonetheless, to improve patient outcomes in these areas, sustained concerted efforts will be required to conduct translational science studies and clinical trials. Importantly, it is anticipated that the development of patient-derived xenograft models in mice will provide additional insights on Asian-centric lymphoma including NKTCL and MEITL [44]. Given that these tumors are rare, there thus arises an excellent opportunity

for collaborative discovery and an international cooperative effort to devise novel therapeutic strategies against them.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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