



Contents lists available at ScienceDirect

# The Lancet Regional Health - Western Pacific

journal homepage: [www.elsevier.com/locate/lanwpc](http://www.elsevier.com/locate/lanwpc)

## Commentary

# Paving the path to better understanding T-cell lymphomas: The importance of lymphoma registries

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## ARTICLE INFO

### Article history:

Received 8 March 2021

Accepted 8 March 2021

Available online 13 April 2021

Despite progresses in the field of non-Hodgkin lymphoma, therapy responses and outcomes remain poor for patients with T-cell lymphoma (TCL), especially for those with relapsed and refractory disease [1,2]. Factors such as marked disease heterogeneity, paucity of cases, and a distinct geographic distribution have limited the field's ability to make substantive and innovative advances. Perhaps, the most significant challenge is the absence of TCL-specific regimens, with CHOP-like chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) remaining as the standard of care for peripheral TCL (PTCL) in spite of high relapse rates [2]. Over the past decade, efforts have been made to identify clinical, epidemiologic, host/tumor genomic, and treatment factors that can have an impact on TCL outcomes and to improve survival. The T-cell project [3]; the International Lymphoma Epidemiology Consortium (InterLymph) [4]; the Lymphoma Epidemiology of Outcomes (LEO) [5]; the Comprehensive Oncology Measures for Peripheral T-cell Lymphoma Treatment (COMPLETE) [6]; and the Latin American Group of Lymphoproliferative Disorders (GELL) [7], are examples of these collaborative efforts developed in an attempt to answer relevant questions on the epidemiology, prognosis, and management of TCL.

Using this approach, Yoon, Song, and Kim et al. present the results of the International Cooperative non-Hodgkin T-cell lymphoma (ICT) registry study, the first prospective registry of adult patients with TCL in Asia [8]. Thirty-two institutions from six Asian countries (Korea, China, Taiwan, Singapore, Malaysia, and Indonesia) enrolled patients aged 19 years and older diagnosed with neoplasms of mature T- and NK-cell according to the 2008 World Health Organization (WHO) classification. The objectives of the study were to estimate the relative frequencies, treatment approaches and outcomes of TCL across Asia. A total of

490 patients were enrolled, 4 were excluded for diagnosis of T-cell lymphoblastic leukemia, and 486 were included in the analysis.

What lessons do we take from the epidemiology of the 486 patients who were registered in the ICT study? First, PTCL, not otherwise specified (NOS) was not the most common TCL subtype, but the third ( $n = 101$ , 20.8%); this finding differs of what is known of TCL epidemiology where PTCL-NOS is the most common subtype accounting for up to 35% of cases in North America and Europe [1]. Second, extranodal NK/T-cell lymphoma (ENKTL;  $n = 139$ , 28.6%), and angioimmunoblastic T-cell lymphoma (AITL;  $n = 120$ , 24.7%) were the first and second most common PTCL subtypes, respectively. Third, HTLV-1-associated adult T-cell leukemia/lymphoma (ATLL) was rare ( $n = 2$ , 0.4%) in these Asian countries.

Were outcomes of the patients registered in the ICT study any different of what is known for TCL? In simple terms, no. TCL continues to carry a dismal prognosis. The median overall survival (OS) for the entire cohort was 83.6 months (95% CI 66.7–110.5). ALK-positive ALCL carried the best outcomes whereas PTCL-NOS the worse. Front-line chemotherapy (with or without radiation) was given to 465 patients with mature T- and NK-cell neoplasms. In early-stage ENKTL ( $n = 99$ ), concurrent chemotherapy plus radiation ( $n = 78$ ) demonstrated overall response rates (ORR) of 80% compared to 48% in those treated with chemotherapy only ( $n = 21$ ); improved progression-free survival (PFS) was also observed in the combined modality group (median not-reached, NR versus 68.1 months; 95% CI 2.1–134,  $p = 0.03$ ). In advanced-stage ENKTL ( $n = 33$ ) chemotherapy approaches that included L-asparaginase demonstrated improved ORR compared with regimens without this drug (62% versus 43%). In advanced-stage ENKTL, consolidation with autologous stem cell transplantation (auto-SCT,  $n = 22$ ) also seemed to improve median PFS (NR versus 5.3 months, 95% CI 2.9–7.7,  $p = 0.04$ ). In patients who failed to respond, or relapsed after front-line therapy ( $n = 49$ ), no regimen

DOI of original article: [10.1016/j.lanwpc.2021.100134](https://doi.org/10.1016/j.lanwpc.2021.100134)

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<https://doi.org/10.1016/j.lanwpc.2021.100134>

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(i.e. salvage chemotherapy, anti-PD1/PD-L1) provided any survival benefit. In PTCL (AITL, PTCL-NOS, ALCL), no chemotherapy regimen (i.e. CHOP, or etoposide-based) was superior to others (ORR 60–65%, PFS 16–21 months). Consolidation with auto-SCT was only beneficial in patients who achieved a complete or partial response, with improved PFS and OS. As with ENKTL, patients with refractory or relapsed PTCL had the worse outcomes. Only 8 patients in the ICT study underwent allogeneic-SCT, hence, no conclusion can be provided. However, the outcome for these patients was also poor.

The ICT study has some limitations. First, the lack of a centralized pathology review is an important limitation given the well-known high discordance among centers during the initial TCL diagnosis [9]. Second, ATLL, which has been previously reported to be prevalent TCL in Asian countries [1], was extremely rare in this cohort, which may be a reflection of not including HTLV-1 endemic countries (Japan and India) in this cohort. Third, the authors utilized the 2008 rather than the revised 2016 WHO classification which refines the diagnostic criteria for some entities, and includes genetic/molecular markers with influence on survival. All these factors might have influenced the observed epidemiology and outcomes of the studied cohort [10].

Despite the above limitations, the ICT study provides valuable insights. It raises awareness of the influence of race/ethnicity and environmental exposures (e.g. HTLV-1 infection) on the epidemiology of TCL even in neighboring countries. Although not all Asian countries were represented, the ICT study characterizes the incidence patterns of TCL in this region. Lastly, and most importantly, when viewed in concert with the registries noted above, it exposes and confirms the lack of effective therapies against TCL across racial/ethnic, socioeconomic and regional variations. This study demonstrates the importance of lymphoma registries on (1) improving representation from minority populations to address relevant questions for the reduction of lymphoma care disparities; (2) developing international studies aimed at better understanding the roles of environmental, lifestyle and cultural factors on differences in lymphoma incidences across countries; and (3) engaging the research community to bring cutting-edge research tools to improving therapies and outcomes for TCL patients.

Generalizing this approach can pave the way for international collaboration, data sharing and creativity that can improve outcomes for patients worldwide.

### Declaration of Competing Interest

No financial conflict of interest to disclose.

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