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Commentary

Peripheral T cell lymphoma

Non-Hodgkin's lymphoma (NHL) is the most common haematological malignancy encountered in adults and constitutes a heterogeneous group of clonal lymphoid neoplasms of B cell, T cell and natural killer (NK) cell origin. Based on the World Health Organization (WHO) classification of lymphoid neoplasms, six major categories of lymphoid, histiocytic and dendritic cell neoplasms have been identified[1,2]. These include precursor lymphoid neoplasms (both B and T cell), mature B cell neoplasms, mature T cell and NK cell neoplasms, HL, post-transparent lymphoproliferative disorders and histiocytic and dendritic cell neoplasms[1,2].

B cell lymphoid neoplasms (both precursor and mature) account for 80-90 per cent of all the NHL, while T cell neoplasms (precursor, mature T cell and NK cell neoplasms) are less common and account for approximately 15-20 per cent of the aggressive lymphomas and 5-10 per cent of all NHL[3,4]. However, there is geographical variation in the incidence of these neoplasms, with larger proportions of T cell neoplasms being reported from the Far East and the Asian continent[3].

With regard to the less common T cell and NK cell neoplasms, the vast majority fall into the mature or peripheral category, with the minority being precursor T cell neoplasms, usually in the form of T lymphoblastic leukaemia/lymphoma. Peripheral or mature T cell and NK cell neoplasms include both leukaemias and lymphomas[1]. The leukaemic subtypes are T cell prolymphocytic leukaemia, T cell large granular lymphocytic leukaemia, aggressive NK cell leukaemia and the leukaemic variant of adult T cell leukaemia/lymphoma syndrome (ATLL), while the peripheral or mature T cell lymphomas (PTCL) include (*i*) predominantly nodal mature T cell neoplasms such as angioimmunoblastic T cell lymphoma (AITL), PTCL, not otherwise specified (NOS), both anaplastic lymphoma kinase (ALK)-positive and negative anaplastic large cell lymphoma (ALCL) and the lymphomatous variant of ATLL; (*ii*) predominantly extranodal mature T cell and NK cell neoplasms such as extranodal NK/T cell lymphoma-nasal type (NK TCL), enteropathy-associated T cell lymphoma (EATCL), hepatosplenic T cell lymphoma (HSTCL) and primary cutaneous T cell lymphomas such as mycosis fungoides and its leukaemic variant, Sezary syndrome, as well as other primary cutaneous varieties[1].

Based on the findings of the International T cell Lymphoma Project, the most common varieties of the PTCL were PTCL, NOS (25.9%), AITL (18.5%), NK-TCL (10.4%) and ATLL (9.6%)[5]. ALCL, ALK positive and ALK negative accounted for 6.6 per cent and 5.5 per cent respectively, while EATCL was noted in 4.7 per cent of the patients[5]. The demographic and clinical characteristics of PTCL in this study revealed a male predominance in all the subtypes, and a median age at presentation of 62 yr (with some varieties presenting at a younger age such as ALCL, ALK-positive – 33 yr and HSTCL T-cell lymphoma – 34 yr). In most of the subtypes of PTCL, advanced stage disease (III/IV) was present in more than 50 per cent of the patients, with the exception of nasal NK-TCL (27%) and primary cutaneous ALCL (14%)[5]. In this study, significant bone marrow involvement (>50%) was present in HSTCL only[5].

An intermediate international prognostic score (IPI) of 2 or 3 was seen in the majority of the patients in this study[5]. Although the IPI score is the most commonly used prognostic tool in PTCL, Gutiérrez-García *et al*[6] discussed the utility of four different prognostic tools in PTCL. These include the IPI score, prognostic index for T cell lymphoma (PIT), IPTCLP (International Peripheral T cell Lymphoma Project Score) and modified PIT. With regard to these four scoring systems, all were found to be useful in

the assessment of patient outcomes, with the IPTCLP being the most important predictor of survival[6].

In contrast to mature B cell neoplasms, therapeutic advances in PTCL have generally lagged behind, particularly with regard to the introduction of immunochemotherapy (chemotherapy and monoclonal antibodies), which have impacted significantly and favourably on the prognosis of aggressive B cell lymphomas. As such, PTCL remains a heterogeneous entity with a generally unfavourable prognosis.

In the International T cell Lymphoma Project, the majority of patients with the most common subtypes of PTCL (PTCL, NOS; AITL; ALCL) received anthracycline-based chemotherapy[5]. Radiotherapy was used mostly for patients with primary cutaneous ALCL and nasal NK-TCL[5]. However, with the exception of ALCL, ALK-positive, the majority of patients did not show any significant benefit using an anthracycline-based regimen compared to a non-anthracycline-based regimen[5]. The five-year overall survival (OS) for PTCL, NOS, AITL and NK-TCL was 32 per cent, compared with only 14 per cent for ATLL. ALCL, ALK-positive patients had the best five-year OS of 70 per cent, while ALCL, ALK-negative had an intermediate five-year OS of 49 per cent[5].

The study by Nemani *et al*[7] in this issue is a large, retrospective review of 244 adult patients with PTCL (non-cutaneous), from a single centre in India, over a six-year period (2007-2012). The study showed a higher proportion of PTCL of 25.1 per cent, than is noted in the Western world[3,4]. In comparison to the findings in the International T cell lymphoma Project, there was a younger median age of 45 yr, a similar male predominance, advanced stage disease in the majority of patients, prominent bone marrow involvement not only in HSTCL but also in ATLL, an intermediate IPI score (low and high) in the majority of patients and similar histological subtypes, with PTCL, NOS being the most common subtype (35.7%). However, a higher proportion of ALCL (ALK-negative 21.3%; ALK-positive 8.6%) together with a lower proportion of AITL (11.5%) and ATLL (1.6%) was noted in this study[7]. The majority of patients in this study received an anthracycline-based treatment, with the three-year OS being 33.8 ± 5 per cent[7].

In the current study[7] only a few patients were offered an autologous stem cell transplant (ASCT). High dose chemotherapy followed by ASCT has been used in the setting of chemosensitive relapsed/refractory PTCL, with variable, but generally moderate success[8]. As such, novel approaches to therapy are required to have a significant impact on prognosis and survival in PTCL.

The 2016 revision of the WHO classification[2] draws attention to the significant advances that have occurred with regard to T cell and NK cell neoplasms in relation to new molecular and genetic advances and approaches, which have led to the revision in the WHO classification and introduction of new provisional entities[9,10]. These molecular and genetic advances need to translate into better understanding of the pathobiology and the development of new targets to optimally treat patients with PTCL[2,9,10].

As a result of these new developments, the future appears brighter, with a shift towards the use of novel, targeted and individualized therapies, leading to better survival outcomes[11]. To this end, a number of agents (such as pralatrexate, romidepsin, crizotinib, belinostat and brentuximab vedotin) have been tested and are showing promise in clinical trials[5,11].

***Conflicts of Interest*:** None.

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