

million, with a median onset at 60 years, slight female predominance and almost invariable association with *Helicobacter pylori* infection. Patients typically present with non-specific dyspeptic type symptoms and the diagnosis is made gastroscopically. 80% of patients have Stage I/II disease.

**Pathology:** The pathological appearance is of small- to medium-sized round or minimally irregular cells, with clumped nuclear chromatin, abundant pale cytoplasm and lymphoepithelial lesions. The cells express pan-B markers but are CD5, 10 and 23 negative. The t(11;18)(q21;q21) detectable by FISH is present in up to 50% of cases with PCR-detectable immunoglobulin gene rearrangements in 90% of cases.

**Management:** *H. pylori* eradication is standard treatment for all patients and in those with disease confined to the mucosa and submucosa results in a durable CR in 70% of cases. For persistent or progressive disease chemotherapy with Chlorambucil +/- Rituximab or loco-regional radiotherapy with 20 Gy are standard approaches. There is no evidence that more intensive therapy results in a better outcome. Life long follow-up should include regular endoscopy.

#### Enteropathy-associated T cell lymphoma

**Clinical features:** Coeliac disease (CD) is caused by gluten intolerance resulting in small intestinal sub-villous atrophy and malabsorption of variable severity which is managed with a gluten free diet (GFD). Coeliacs have a 20 fold increased rate of developing lymphoma with 60–75% of them sub-typed as EATCL. Clinical presentation follows 3 patterns (1) development of refractory coeliac disease (RCDII) despite adherence to a GFD (2) acute presentation with gut perforation/acute severe malabsorption despite adherence to a GFD and (3) acute presentation as in (2) with no previous diagnosis of CD. EATCL diagnosis can be challenging as it is usually confined to the small intestine and tissue is usually obtained surgically or by endoscopy (gastroscopy/double balloon enteroscopy).

**Pathology:** EATCL is characterised by a monomorphic population of medium to large cells with round or angulated vesicular nuclei, prominent nucleoli and moderate to abundant, pale-staining cytoplasm with expression of CD3<sup>+</sup>, CD5<sup>+</sup>, CD7<sup>+</sup>, CD8<sup>+/−</sup>, CD4- and CD103<sup>+</sup>.

**Management:** The 5 year OS is 20% with conventional chemotherapy and this poor outcome is thought to be related to poor patient performance status secondary to nutritional deficiency/gastrointestinal surgery and the chemo-refractoriness inherent to T-cell lymphomas. Outcome can be improved using intensive nutritional support and primary chemotherapy followed by an autologous transplantation for patients under the age of 65 resulting in a 5 year OS of between 50–60%.

**Refractory coeliac disease:** Patients who are diagnosed with an RCDII prodrome are interesting both for insights into EATCL lymphomagenesis and also because they may respond to less intensive therapy, thus reducing the risk of EATCL transformation. RCD II is characterised by sub-villous atrophy, loss of CD8 intra-epithelial lymphocytes and clonal

T-lymphocytes with 70% progression to EATCL within 5 years. A small study of patients with RCDII who responded to Cladribine therapy had a 5 year OS of 83% which may be improved further by autologous SCT.

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#### MATURE T- AND NK- CELL NEOPLASMS

*C. Dearden*

*Royal Marsden Hospital NHS Foundation Trust,  
London, United Kingdom*

Correspondence: [claire.dearden@rmh.nhs.uk](mailto:claire.dearden@rmh.nhs.uk)

The mature or peripheral T-cell neoplasms are a biologically and clinically heterogeneous group of rare disorders that result from clonal proliferation of mature post-thymic lymphocytes. Natural killer (NK) cells are closely related to T cells and neoplasms derived from these are therefore considered within the same group. The World Health Organization (WHO) classification of haemopoietic malignancies has divided this group of disorders into those with predominantly leukaemic (disseminated), nodal, extra-nodal or cutaneous presentation. Within the WHO classification these malignancies are differentiated on the basis not only of clinical features but also of morphology, immunophenotype and genetics.

The mature T-cell and NK-cell neoplasms account for approximately 10–12% of all lymphoid malignancies, usually affect adults and most of the entities described are more commonly reported in males than in females. The median age at diagnosis for the group as a whole is 61 years with a range of 17–90 years. There is geographical variation in the frequency of the different subtypes and in Europe peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angio-immunoblastic T-cell lymphoma (AITL) account for

about three quarters of all cases. NK-cell lymphomas (NKTCL) are more common in Asia and are associated with Epstein-Barr virus (EBV). The human T-cell leukaemia virus (HTLV-I) is aetiologically linked to adult T-cell leukaemia/lymphoma (ATLL).

Although some may follow a relatively benign protracted course, most have an aggressive clinical behaviour and poor prognosis. Excluding anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and indolent mycosis fungoides (MF), which have a good outcome, 5 year survival for other nodal and extranodal T-cell lymphomas is about 30%. The similarity between progression free survival (PFS) and overall survival (OS) is an indication of the poor response to second line therapies. The rarity of these diseases and the lack of randomized trials mean that there is no consensus about optimal therapy for T- and NK-cell neoplasms.

**Presentation, diagnosis, staging and prognosis.** Extranodal presentation is common in PTCL and this often contributes to a delay in diagnosis. When compared to aggressive B-cell lymphomas, patients tend to present with unfavourable international prognostic index (IPI) scores (> 3), more advanced disease, a poorer performance status and an increased incidence of B symptoms. Paraneoplastic features are well described including eosinophilia, haemophagocytic syndrome and autoimmune phenomena. The latter are particularly seen in AITL.

**Diagnosis** is based on examination of peripheral blood or tissue biopsy for histological features supplemented by detailed immunohistochemistry, flow cytometry, cytogenetics and molecular genetics. Expert haematopathology review is essential for the correct classification of the different subtypes. Unlike B-cell lymphomas, there is no simple test for clonality and this should be established by polymerase chain reaction (PCR) for rearrangement of T-cell receptor genes.

**Staging** is as for all lymphomas, including tests to assess the extent of disease (e.g. imaging and bone marrow biopsy) and to identify the features needed to assign a prognostic score. Investigations include full blood count and differential, tests of renal and hepatic function, lactate dehydrogenase (LDH), beta2 microglobulin, albumin, serum calcium, uric acid, bone marrow core biopsy, chest X-ray and computerized tomography (CT) scan of chest, abdomen and pelvis. The role of <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scanning in PTCL is under investigation and has only been reported in the clinical evaluation of patients in a limited number of clinical studies so far. The data suggest that most T-cell lymphomas are FDG-avid although with variable intensity but that in CTCL PET is not sufficiently sensitive or specific. However, in PTCL stage was altered in less than 10% and did not change treatment recommendations. It cannot be recommended yet for routine use and must be prospectively validated in trials.

Lumbar puncture and magnetic resonance imaging (MRI) of the brain are only required if there is any clinical

suspicion of central nervous system (CNS) involvement. The International Prognostic Index (IPI) gives useful prognostic information in PTCL but it clusters many cases in the higher risk groups. Newer T-cell specific prognostic scores (e.g. PIT) appear to be more discriminatory and may be valuable in prospective trials.

**Treatment.** Treatment of all T and NK neoplasms should be within the context of a clinical trial if possible as standard therapy gives disappointing results. Outside trials, CHOP remains the standard first-line therapy for most nodal and extra-nodal subtypes with no clear evidence that alternative or more intensive regimens are more effective. Consideration should be given to consolidation with autologous haemopoietic stem cell transplantation (HSCT), especially in high-risk chemo-sensitive disease and AITL where results appear to be superior. Relapsed or refractory disease should be treated with relapse-schedule chemotherapy with consideration of allogeneic-HSCT (with reduced intensity conditioning) or autologous stem cell transplantation if the disease is chemosensitive. A number of newer agents show promise, particularly gemcitabine (alone and in combination), pralatrexate and romidepsin. Lenalidomide, bendamustine and bortezomib have also shown efficacy.

CNS prophylaxis should be considered using the same criteria as for diffuse large B-cell lymphoma.

**Specific subtypes.** For most subtypes their rarity has meant that there is little evidence to determine the best therapy. For some, however there is emerging data that specific tailored sub-type approaches are beneficial, and some examples are given below.

**T-PLL** should be treated with intravenous alemtuzumab followed by autologous or allogeneic stem cell transplant in first remission. Purine analogues may be helpful in resistant cases.

**T-LGL Leukaemia** is an indolent condition which does not always require treatment. Therapy is indicated for severe or symptomatic cytopenias and relies on immune-modulatory therapies such as oral cyclosporine, weekly oral low-dose methotrexate or low-dose cyclophosphamide. Second line treatments include purine analogues and alemtuzumab. Chronic lymphoproliferative disease of NK cells should be managed as for T-LGL. Rare aggressive NK-cell leukaemias occurring in younger adults require a different therapeutic approach (ALL-type chemotherapy) and consideration of stem cell transplantation.

**ATLL** is mainly seen in far eastern (Japanese) and Afro-Caribbean patients. Several subtypes exist and the smouldering/chronic subtypes may not initially require treatment although they may benefit from anti-retroviral therapy. The acute and lymphoma subtypes, have very poor prognosis and are usually managed with multi-agent chemotherapy regimens followed by allogeneic HSCT where possible. Recent evidence suggests that these patients benefit from anti-viral drugs given concomitantly, sequentially or instead of chemotherapy. Novel therapies e.g. anti-CCR4 are being evaluated.

**ALCL** (particularly ALK+) has the best outcome with conventional CHOP. Relapsed patients have achieved very high response rates with a CD30-targeted immune-conjugate, brentuximab vedotin. This may be effective in other CD30-positive PTCL and is currently being evaluated in combination in the front-line setting.

**Extranodal Nasal NK/T cell lymphoma** occurs most commonly in Asian populations and is EBV positive. The distinction at diagnosis between localized and disseminated disease is important as the latter has a dismal prognosis. Outcome is unsatisfactory with CHOP-like therapy and asparaginase-containing regimens are preferred. High dose radiotherapy (50–55 Gy) is very important in the control of localized disease and contributes significantly to cure of patients with limited stage at presentation.

**EATL** patients often present acutely and with poor PS. It is important to liaise with an experienced gastroenterologist to assist with biopsy, staging and follow up and to manage nutritional problems. CHOP-like or intensified therapy, with an up-front autograft remains a common approach and does appear to be superior to **CHOP** alone in retrospective series.

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