Updates: Minor changes

Introduction

T-cell neoplasms are a heterogeneous group of neoplasms derived from post-thymic lymphoid T-cells at different steps in differentiation [1]. NK-cell neoplasms are closely related both clinically and immunophenotypically therefore they will be grouped together. This group of lymphomas is uncommon in North America, constituting 15-20% of non–Hodgkin’s lymphomas [2]. In comparison to large cell lymphomas of B-cell origin, PTCL have a different spectrum of clinical features with more extranodal manifestations, advanced stage at presentation and overall more aggressive disease with poor response to standard therapy [3-5].

WHO Classification [6]

<table>
<thead>
<tr>
<th>Nodal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral T-cell lymphoma unspecified</td>
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<tr>
<td>Anaplastic large cell lymphoma</td>
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<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Extranodal</td>
</tr>
<tr>
<td>NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Hepatosplenic γ/δ T-cell (provisional)</td>
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<tr>
<td>Enteropathy type T-cell lymphoma</td>
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<tr>
<td>Blastic NK-cell lymphoma</td>
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<tr>
<td>Leukemia/Disseminated</td>
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<tr>
<td>Adult T-cell leukemia/lymphoma</td>
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<tr>
<td>Aggressive NK cell Leukemia</td>
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<tr>
<td>T-cell prolymphocytic leukemia</td>
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<tr>
<td>T-cell large granular lymphocytic leukemia</td>
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<tr>
<td>Cutaneous (see Primary Skin Lymphomas)</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>Lymphomatoid papulosus</td>
</tr>
<tr>
<td>Large cell lymphoma</td>
</tr>
</tbody>
</table>
## Staging

Patients with T-cell Lymphoma should be staged according to both the Ann Arbor and IPI systems.

### Ann Arbor Stage

#### Stage Definition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region or a single extranodal site.</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph nodes on the same side of the diaphragm or localized involvement of an extra lymphatic organ or site and one or more lymph nodes on the same side of the diaphragm.</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm that may also be accompanied by involvement of the spleen or by localized involvement of an extra lymphatic organ or site or both.</td>
</tr>
<tr>
<td>IV</td>
<td>Diffused or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.</td>
</tr>
</tbody>
</table>

The absence or presence of fever > 38.5 °C, drenching night sweats, and/or unexplained weight loss of 10 percent or more body weight in the six months preceding admission are to be denoted in all cases by the suffix A or B respectively.

### The International Prognostic Factor Index

The International Prognostic Index (IPI) which has been shown to significantly predict outcome in aggressive B-cell lymphomas has also been demonstrated to have similar prognostic importance in individuals with T-cell lymphomas [3, 7] as illustrated in the graphs on pages 3-4. The IPI index is dependent on five prognostic factors: age, Ann Arbor stage, performance status, LDH and number of extranodal sites.

**INTERNATIONAL INDEX < 3**

Overall Survival

- B
- T

(P=0.001)

**INTERNATIONAL INDEX > 2**

Overall Survival

- B
- T

(P=0.044)
Figure 4. Survival of 95 patients with peripheral T-cell lymphoma unspecified according to the initial Ann Arbor stage ($P < 0.01$).

Figure 5. Survival of 95 patients with peripheral T-cell lymphoma unspecified according to the International Index for Aggressive Lymphomas: low risk (L), low/intermediate risk (L/I), high/intermediate risk (H/I), and high risk (H) ($P < 0.001$).
Baseline Investigations

The following baseline investigations are indicated for most patients with T-cell lymphomas:

- Pathology review
- CBC, differential, blood film
- Serum electrolytes and creatinine
- Liver function tests
- Serum LDH, Serum uric acid
- Chest x-ray
- CT chest, abdomen and pelvis (CT head & neck if appropriate)
- Unilateral bone marrow biopsy

Gallium Scans

A total body gallium scan should be performed in all patients being treated with curative intent, particularly those who would be considered for salvage therapy and stem cell transplantation if not in complete remission after initial therapy.

HIV Serology

Patients should be questioned regarding risk factors including blood transfusion, intravenous drug use and sexual contact. Those patients felt to be at risk should be tested.

CSF Analysis

A lumbar puncture to evaluate leptomeningeal involvement with lymphoma should be performed in patients with:

- HIV positivity
- Paraspinal, sinus or vertebral involvement
- Elevated LDH and > 1 extra nodal sites
- Unexplained neurological symptoms
- HTLV-1 associated T-cell lymphoma

Cardiac Assessment

A cardiac assessment should be performed in all patients potentially eligible for anthracycline-based therapy. MUGA or 2D-echocardiogram should be performed in all patients with a history of:

- Age > 60
- Hypertension
- Congestive heart failure
- Peripheral vascular disease
- Angina
- Cardiac arrhythmia
- Myocardial Infarction

Anthracyclines should be used with caution in patients with an EF < 45%, recent MI (< 3 months) or severe arrhythmia.
Peripheral T-Cell Lymphoma Unspecified

Introduction
Among peripheral T-cell lymphomas the unspecified group constitutes the most common subtype [1, 5]. This subtype tends to occur in older patients presenting with more advanced stage, extranodal involvement, especially in the skin, and constitutional symptoms. Overall and failure free survival is poor.

Baseline Investigations – see page 5

Diagnosis
An adequate tissue sample is required for histology and immunocytochemistry. Morphology is variable, comprising medium to large cells expressing variable pan T-cell markers, although most will express CD4 or CD8, but not both. T-cell receptor genes are usually rearranged [8].

Prognosis
The median survival of individuals with PTCL unspecified is 22 months with a 4-year actuarial survival of 32% [1]. The most important prognostic factors predicting response and survival in this subtype is the presence of B symptoms and the International Index [1].

Treatment
A complete response rate of around 47% can be achieved when patients with PTCL unspecified are treated with CHOP chemotherapy [1, 9]. However, less than 30% of patients with high, high/intermediate, or low/intermediate risk are alive at 5 years after diagnosis indicating that CHOP chemotherapy is inadequate in this subtype [1]. However, until better regimes are developed, patients will be scheduled to receive 6-8 cycles of CHOP at three weekly intervals. Response will be assessed clinically at each visit. Repeat imaging should be performed following the third and sixth cycle of CHOP. Patients should be considered for enrollment in available clinical trials or in younger patients, high dose therapy with stem cell support [5, 10-12]. The role of monoclonal antibodies such as Campath is yet to be clarified, but under ongoing investigation [13, 14].

The role of Alemtuzumab (Campath®) in addition to CHOP in patients with PTCL is currently being explored. In phase II trials it does appear that the combination therapy results in improved response rates up to 75% and overall survival of 50% at 2 years. The combination is tolerated, however there is an increase in myelosuppression and opportunistic infections particularly CMV reactivation therefore surveillance and prophylaxis with Septra and acyclovir is required. Given the small series and increased toxicity this combination therapy should be given in the context of a clinical trial. Currently Alemtuzumab is not approved for combination therapy [15].
Management of Localized Disease

There is little information in the literature on how to manage localized Stage I and II PTCL unspecified. This reflects the fact that most patients with PTCL present with advanced stage disease. As a group, peripheral T-cell lymphomas have a poorer outcome than diffuse large B-cell lymphomas (DLBCL), especially in patients with advanced stage disease, but as of yet there is no evidence that treating PTCL with more aggressive regimens than CHOP will provide any survival advantage. Additionally, the IPI has similar prognostic significance in PTCL as it does in DLBCL. Therefore patients with localized disease and a favorable IPI score should be considered for combined modality therapy as in **Localized Diffuse Large B-Cell Lymphoma**.

### Anaplastic Large Cell Lymphoma

ALCL accounts for approximately 5% of all adult NHL. This subtype of lymphoma tends to occur in younger patients with a male predominance and has the best overall survival rate of any large cell lymphoma. Most cases of ALCL present as primary disease, however, rarely patients have a history of a previous lymphoma such as mycosis fungoides or Hodgkin’s disease [16, 17]. For patients with isolated skin ALCL, see the Skin Lymphoma Treatment Policy.

### Baseline Investigations – see page 5

### Diagnosis

An adequate specimen of involved tissue is required. Anaplastic large cell lymphoma must be distinguished from metastatic carcinoma and Hodgkin’s disease, as the malignant lymphocytes can be variable in morphology. This subtype is characterized by the proliferation of large pleomorphic lymphoid cells, which strongly express CD30 antigen (Ki–1 antigen), and preferentially spread in lymph node sinuses [8, 18]. The majority of cases are of mature T-cell lineage with variable expression of CD3 and CD4. Occasionally ALCL cells lack T- or B-cell markers and are considered null cell type. TCR genes are usually rearranged [8]; B-cell phenotype is seen in less than 20% of cases. Approximately, two third of cases of ALCL are found to over-express ALK1. The majority of these are associated with the t(2;5)(p23;q35) chromosomal translocation leading to the formation of a chimeric NPM - ALK protein (NPM – nucleoplasmin on chromosome 5 – ALK – anaplastic lymphoma kinase – chromosome 2). This translocation leads to constitutive activation of the ALK tyrosine kinase protein leading to the terminology of ALK1+ ALCL. There have been several other chromosomal abnormalities described involving the ALK locus also leading to its over expression, of ALK making up approximately 20% of ALK1+ ALCL [19-21].

<table>
<thead>
<tr>
<th>Clinical Subtypes [22]</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALK + / systemic</strong></td>
<td>Young patient, male predominance, extranodal disease T-cell/Null cell phenotype, variable histology, good prognosis</td>
</tr>
<tr>
<td><strong>ALK - / systemic</strong></td>
<td>Older, tends to occur in association with other lymphoproliferative disorders, poor prognosis</td>
</tr>
<tr>
<td><strong>ALK - / primary skin</strong></td>
<td>CD30+, excellent prognosis (see Primary Skin Lymphoma)</td>
</tr>
</tbody>
</table>
**Prognosis**

Anaplastic large cell lymphoma has a 5-year overall survival rate of approximately 65%, which is better than that of most other subgroups of T or B cell lymphoma. Several studies have identified that patients who express the t(2;5) chromosomal translocation (ALK+ lymphoma) have a superior 5-year overall survival between 70-93%, as compared to ALK- patients whose 5-year survival ranges from 15-40% [23-25].

The International Prognostic Index and serum LDH level have also been reported as independent variables to predict survival [23, 24]. Patients with systemic ALCL and skin involvement appear to have a higher failure rate, but similar overall survival [26, 27].


**Treatment**

ALCL demonstrates higher CR rates (approximately 70%) than other subtypes of T-cell lymphoma and should be treated as outlined for Diffuse Large B-Cell Lymphoma [27, 28].

**Localized Disease I-IIA**

If patients are ALK+ and non-bulky, patients should be considered for combined modality therapy. Three cycles of CHOP should be administered at three weekly intervals. Response will be assessed by CT scan 3-4 weeks following the third cycle.

Patients in CR following chemotherapy will receive **3000 cGy in 15 fractions**. If residual disease is documented after chemotherapy, sites of residual disease will be boosted to **3600 cGy in 18 fractions**.

Patients with ALK- stage I-IIA should be treated with full 6 cycles of CHOP given their overall poorer prognosis.
Advanced Disease III-IV

Patients will be scheduled to receive 6 cycles of CHOP at three weekly intervals. Response will be assessed clinically at each visit. Patients will have repeat imaging following the third and sixth cycle of CHOP.

Relapsed Disease

Patients with relapsed disease should be treated as outlined for Diffuse Large B-cell Lymphoma. Autologous transplantation should be recommended in those patients under the age of 65 with good performance status and no limiting comorbid medical problems who respond to salvage chemotherapy. DHAP is to be given as first-line salvage therapy. Involved field radiation should be considered for patients with localized relapse in whom stem cell transplantation is not possible.

Angioimmunoblastic Lymphoma (AILD)

Introduction

This is a rare lymphoproliferative disorder, accounting for 1-2% of all non-Hodgkin lymphomas, characterized by lymphadenopathy, fever, skin rash, hepatosplenomegaly, opportunistic infections, hemolytic anemia and polyclonal hypergammaglobulinemia. EBV positive B cells are typically found in all cases of AILD pointing to the likelihood that EBV has a pathogenic role in this disease [29].

Baseline Investigations

The following baseline investigations are indicated for most patients with AILD:

- Pathology Review
- CBC, differential, blood film
- Serum electrolyte and creatinine
- Liver function tests
- Serum LDH
- Serum uric acid
- Direct Coombs test
- Serum protein electrophoresis, serum immunoglobulins
- Chest x-ray
- CT chest, abdomen and pelvis (CT head & neck if appropriate)
- Unilateral bone marrow biopsy

Gallium scans, CSF analysis, HIV serology, and cardiac assessment (see page 5)

Diagnosis

A diagnosis of AILD requires the examination of an adequate specimen of tissue. The node architecture is effaced with prominent neovascularization and an infiltration of immunoblasts, lymphocytes, and plasma cells. Tumor cells express T-cell associated antigens CD3 and are typically CD4 positive. Tumour cells also produce high levels of CXCL13 and express CD10 and usually BCL6 and thus are felt to be T follicular helper cells of germinal center origin. T-cell receptor rearrangement is demonstrated in 75% of cases [8]. Typical cytogenetic findings are trisomy 3, trisomy 5, and gain of an X chromosome [30]. B cell clonality can also be seen in AILD, either due to stimulation from CXCL13 or from EBV antigenic stimulation [30, 31].
Prognosis

This is an aggressive lymphoma with median survival rates ranging from 12 to 24 months [32-34]. The major cause of mortality is infection. Prognostic factors that may correlate with poor prognosis include history of drug exposure, skin rash, lymphopenia and more recently the presence of abnormal cytogenetic findings [35-37]. However, due to limited experience, these factors cannot be used to predict clinical course or guide treatment.

Treatment

The treatment of AILD has been unsatisfactory with approximately 25% of patients achieving complete and sustained remission with combination chemotherapy [29]. There are a limited number of small studies reported in the literature outlined below:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Therapy</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nathwani 1978 [38]</td>
<td>None</td>
<td>4</td>
<td>21</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>N=48</td>
<td>Prednisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined chemotherapy (w/o A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pangalis 1983 [33]</td>
<td>None</td>
<td>7</td>
<td>17</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>N=41</td>
<td>Prednisone</td>
<td>16</td>
<td>16</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Combined chemotherapy (w/o A)</td>
<td>13</td>
<td>13</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Tobinai 1988 [32]</td>
<td>None</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=36</td>
<td>Prednisone</td>
<td>11</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined chemotherapy (w/o) A</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Combined chemotherapy with A</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Siegert 1992 [34]</td>
<td>Prednisone</td>
<td>28</td>
<td>28</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>N=39</td>
<td>Combined chemotherapy with A</td>
<td>11</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Pautier 1999 [39]</td>
<td>Prednisone</td>
<td>8</td>
<td>8</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>N=33</td>
<td>Combined chemotherapy with A</td>
<td>25</td>
<td>25</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

A = Adriamycin

Treatment Options

A conservative “watch and wait” approach may be adopted in those patients who are asymptomatic and lack demonstrable clonality in the lymph node biopsy.

Systemic Therapy

- Combination chemotherapy (CHOP) should be considered first-line in symptomatic patients as it appears to improve median survival. Six cycles of CHOP (Appendix B) should be administered at 3 weekly intervals. Response will be assessed clinically at each cycle and by CT scan after the third cycle and sixth cycle.
- Prednisone at a dose of 2 mg/kg orally x 4 to 8 weeks continued for 2 weeks following remission followed by a 4 to 6 week taper can be used in patients who are not felt to be candidates for CHOP chemotherapy.

Young patients should be considered for high dose therapy with stem cell support in first remission due to the poor prognosis of AILD.

Refractory or Relapsed Disease

A number of agents including: **Cladribine** [40], **interferon α** [41], **cyclosporin** [42], **fludarabine** [43] and **alemtuzumab** [44] have been reported to induce remission in small series of patients with refractory AILD. Any of the above agents can be tried in refractory patients. We would suggest using the agent you are most familiar with as there is not enough evidence to support one over the other.
Extranodal NK/T-Cell Lymphoma, Nasal Type

Introduction

Real Classification: Angiocentric T-cell Lymphoma

NK/T-Cell nasal type lymphoma is a rare entity associated with a poor prognosis especially in those individuals with advanced disease. This subtype of lymphoma primarily presents in extranodal sites, most commonly the nose, skin or gastrointestinal tract [45] and may be associated with a hemophagocytic syndrome [8].

Baseline Investigations – see page 5

Diagnosis

The diagnosis of NK/T cell nasal type lymphoma requires an adequate biopsy of involved tissue. Histologically it is characterized by angiocentric, polymorphous lymphoid infiltrates with necrosis of both tumor and surrounding normal tissues. Erythrophagocytosis by benign histiocytes may also be seen. The natural killer cell markers CD56 and CD2 are expressed in 80%, where T cell markers are found in 10–30%. Typically there is no rearrangement of the TCR or Ig genes. The EBV virus can be demonstrated in tumor cells in 95% of cases [6, 8, 46].

Prognosis

Prognosis is variable with long term survival in stage 1 non-bulky disease reported ranging from 20-80%. Systemic progression is invariably rapidly fatal [47, 48].

**Treatment**

Due to the rarity of this disorder there has not been a general consensus regarding optimal management of this lymphoma subtype. The literature in this area is mainly retrospective and includes B-cell nasal lymphoma along with T-cell and NK cell subtypes.

**Limited Stage Disease IIE-IIE**

The main modality of treatment prior to 1980 was local radiation, however local failure occurred in 15-20% of patients with nasal T-cell lymphoma, accounting for up to 70% of recurrences after complete remission. Since 1980 combination chemotherapy with involved field radiation has been considered superior to radiation alone in most series of patients [49-52]. However there have been two studies Liang et al. [47] and Cheung et al. [53] that have not demonstrated a significant improvement in overall survival with combined modality therapy of chemotherapy followed by radiation versus radiation alone. This was mainly due to locally progressive disease while on chemotherapy. Therefore, in patients with truly limited stage disease it may be prudent to consider radiation therapy **(4400 cGy in 22 fractions)** up front, followed by of six cycles of CHOP (Appendix B) to be administered at 3 weekly intervals.

**Advanced Stage Disease**

Patients with stage III-IV disease almost uniformly die despite aggressive therapy. Treatment consists of combined modality therapy with CHOP followed by involved field radiation to the involved nasal area. 6-8 cycles of CHOP (Appendix B) should be administered at 3 weekly intervals. Response will be assessed clinically at each cycle and by CT scan after the third cycle and sixth cycle. There is some evidence that the addition of L-asparaginase to combination chemotherapy may result in better long-term outcomes [54].

**Autologous Transplantation**

As this disease is invariably fatal in advanced stages or in relapse, young patients with a favorable response to combined modality therapy should be considered for high-dose therapy with stem cell support in first remission [55-57].

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**Fig 4. Overall survival by stage and immunophenotype.**

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CNS Prophylaxis

Traditionally, patients with nasal lymphoma have received CNS prophylaxis. However, recent literature does not support a predilection for CNS spread in those patients treated with combined modality therapy without CNS prophylaxis [47, 51]. CNS relapse appears to more reflective of either systemic lymphoma progression or local failure [51]. Therefore, CNS prophylaxis does not appear to be required.

Relapsed Disease

Patients with relapsed disease should be treated as outlined for Diffuse Large B-Cell Lymphoma (see Diffuse Large B-Cell Lymphoma). Autologous transplantation should be recommended in those patients under the age of 65 with good performance status and no limiting comorbid medical problems who respond to salvage chemotherapy. Involved field radiation should be considered for patients with localized relapse in whom stem cell transplantation is not possible. Other non-transplant eligible patients should be managed palliatively.

Hepatosplenic Gamma/Delta T-Cell Lymphoma

Introduction

This is an extremely rare subtype of T-cell lymphomas, typically occurring in younger patients who present with hepatosplenomegaly, bone marrow involvement and thrombocytopenia and often peripheral blood involvement [58].

Baseline Investigations – see page 5

Diagnosis

Diagnosis requires a sufficient sample of involved organs. Monotonous medium sized cells typically infiltrate liver, spleen and sometimes marrow in a sinusoidal pattern. These lymphoid cells generally demonstrate a gamma/delta phenotype: CD3+, CD2+, CD4-, CD5-, CD8- and TCR γδ gene rearrangement [8]. Almost all cases have abnormalities of isochrone 7 and trisomy 8 [59].

Treatment

This entity is treated as outlined for Diffuse Large B-Cell Lymphoma. Patients usually relapse despite initial response to chemotherapy. However, until better regimes are developed, patients will be scheduled to receive 6-8 cycles of CHOP at three weekly intervals. Patients should be considered for enrollment in available clinical trials, or in younger patients, high dose therapy with stem cell support.
Enteropathy Type T-Cell Lymphoma

Introduction

Approximately 10% of intestinal lymphomas have a T-cell immunophenotype [60]. Individuals often have a history of gluten sensitive enteropathy or malabsorption and frequently present with weight loss, abdominal pain, diarrhea or bowel obstruction.

Baseline Investigations – see page 5

Diagnosis

Clinically these lymphomas appear as ulcerated plaques or strictures in the proximal jejunum, however other regions in the stomach, small and large bowel have been described [61]. Surgery is usually required to establish diagnosis and avoid perforation during therapy. Tumor cells range from small, medium mixed to large or anaplastic lymphoid cells. The adjacent mucosa contains a high number of intraepithelial T-cells. Lymphoid tumor cells demonstrate the following immunophenotype: CD3+, CD4-, CD5-, CD7+, CD8+/ CD103+ (mucosa lymphocyte antigen). TCR genes are rearranged [8]. Chromosomal abnormalities are often found, typically gains or losses in chromosomes, the most common being gain in 9p33-q34, which is very rare in other types of T-cell lymphomas [62].

Treatment

Patients have a poor outcome with a 5-year survival of 25% [61]. Therapy for intestinal T-cell lymphoma involves surgical resection of the primary lesion due to a high rate of gastrointestinal complications with chemotherapy alone. Following surgery, patients should receive 3 to 6 cycles of CHOP chemotherapy at 3 weekly intervals. If a short course of chemotherapy is planned then whole abdominal radiation at a dose of 2500 cGy in 20 fractions should be added.

Blastic NK-Cell Lymphoma

Introduction

Blastic NK-Cell lymphoma is a very rare predominately extranodal lymphoma, particularly involving the skin. Most patients have disseminated disease at presentation with lymph nodes, skin, bone marrow and peripheral blood involvement [6, 63].

Baseline Investigations – see page 5

Diagnosis

The diagnosis of NK-cell blastic lymphoma requires the examination of an adequate specimen tissue. The morphology is typically diffuse monotonous infiltration of medium sizes cells with immature features. There is often necrosis and angiocentric infiltration. Tumour cells express CD56 and CD4 and are negative for CD3, CD30 and CD33. This entity has been recently reclassified as CD4+/CD56+ hematodermic neoplasm as there
is evidence that the malignant cells arise from type 2 dendritic cells. There is no TCR gene rearrangement found, and specimens are typically EBV negative [6, 63, 64].

### Prognosis

Blastic NK-cell lymphoma is a very aggressive malignancy with poor response to traditional lymphoma type regimens.

### Treatment

Given the rarity of this lymphoma, there is no consensus on the management of this lymphoma subtype. There is no evidence that they will respond any better to more aggressive lymphoma regimens than they will to CHOP, therefore, they should be treated according to the guidelines for **Diffuse Large B-cell Lymphoma**. Patients who are eligible should be considered for allogeneic stem cell transplant [64].

### Adult T-Cell Lymphoma/Leukemia

#### Introduction

Adult T-cell lymphoma/leukemia is etiologically linked to the human T-cell lymphotrophic virus type-1 (HTLV-1). HTLV-1 is a retrovirus endemic in southwestern Japan, Caribbean, and Southwestern United States. Between 1-5% of individuals infected with the virus will develop T-cell leukemia/lymphoma with an average latency period of more than 30 years [65, 66].

#### Baseline Investigations – see page 5

#### Diagnosis

The blood film in ATLL often demonstrates characteristic lymphocytes with polylobulated nuclei or flower cells. The lymph node histology is usually that of a diffuse T-cell lymphoma of immunoblastic or pleomorphic subtype and is often indistinguishable from non HTLV-1 associated T-cell non-Hodgkin's lymphoma. The ATLL cells exhibit the following immunophenotype: TdT, CD2+, CD5+, and CD7-. Approximately, 90% of cases are CD4+ and CD8- with rare cases co-expressing both CD4 and CD8 or are negative for both. The majority of cases are CD25+, which corresponds to the α peptide chain of the interleukin-2 receptor. Patients must also demonstrate antibodies to HTLV-1 as well as the presence of clonally integrated HTLV-1 DNA into the cellular DNA of neoplastic T-cells [6, 67].

#### Clinical Subtypes

Adult T-cell lymphoma/leukemia is a heterogeneous disease that has been classified into four main categories [67].

- Smoldering
- Chronic
- Lymphoma
- Acute
Their diagnostic criteria are summarized in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Smoldering</th>
<th>Chronic</th>
<th>Lymphoma</th>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HTLV-1 antibody</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>&lt; 4</td>
<td>≥ 4</td>
<td>&lt; 4</td>
<td>+ / -</td>
</tr>
<tr>
<td>Abnormal T lymphocytes</td>
<td>≥ 5%</td>
<td>+</td>
<td>≤ 1%</td>
<td>+</td>
</tr>
<tr>
<td>Flower cells</td>
<td>Occasionally</td>
<td>Occasionally</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Calcium</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal/raised</td>
<td>Normal/raised</td>
</tr>
<tr>
<td>LDH</td>
<td>&lt; 1.5 x normal</td>
<td>&lt; 2 x normal</td>
<td>Normal/raised</td>
<td>Normal/raised</td>
</tr>
<tr>
<td>Nodes</td>
<td>No</td>
<td>+ / -</td>
<td>Yes</td>
<td>+ / -</td>
</tr>
<tr>
<td>Liver/Spleen</td>
<td>No</td>
<td>+ / -</td>
<td>+ / -</td>
<td>+ / -</td>
</tr>
<tr>
<td>Skin</td>
<td>+ / -</td>
<td>+ / -</td>
<td>+ / -</td>
<td>+ / -</td>
</tr>
<tr>
<td>Bone lesions</td>
<td>No</td>
<td>No</td>
<td>+ / -</td>
<td>+ / -</td>
</tr>
<tr>
<td>Marrow involvement</td>
<td>No</td>
<td>No</td>
<td>+ / -</td>
<td>+ / -</td>
</tr>
</tbody>
</table>

**Prognosis**

The survival of patients with acute and lymphoma subtypes of ATLL is poor as outlined in the following table [67].

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>24.3</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10.2</td>
</tr>
<tr>
<td>Acute</td>
<td>6.2</td>
</tr>
</tbody>
</table>

However, there may be considerable variation in prognosis within clinical subtypes. Five other prognostic variables were found by the Lymphoma Study Group to be predictive of shortened survival: poor performance status, high LDH, age > 40 yr., increased tumor bulk and hypercalcemia [68].

**Treatment**

**Chronic and Smoldering**

In these subtypes of ATLL, a “watch and wait” approach may be taken. Some individuals may not require treatment for months to years. Generally, patients are treated at evidence of disease progression to acute or lymphomatous forms. Patients with symptomatic smoldering ATLL can be considered for therapy with interferon and zidovudine or single agent alkylators.

**Acute/Lymphoma**

The treatment of patients with the acute or lymphomatous forms of ATLL remains disappointing. Despite wide experience with the disease in Japan and the Caribbean, there is no consensus on the best available therapy for ATLL. Anthracycline-based regimes are associated with CR rates of 17-20% [68]. Improved response rates are obtained with intensification of chemotherapy, CR 42%, however, median survival remains unchanged at 6 months [68, 69]. The CNS appears to be an important site of relapse in ATLL and may act as a sanctuary site. CNS involvement is clinically evident in 2.5% of patients at diagnosis. In one study, 9/19 patients who had not received prophylactic therapy demonstrated meningeal involvement at relapse [70]. Therefore, all patients should have a CSF sample analyzed at diagnosis and receive prophylactic intrathecal methotrexate in addition to combination chemotherapy. Prevention of infection is also an important component of therapy as severe infections leading to death can occur in up to 50% of patients [68]. All patients should therefore receive prophylactic Septra during therapy.
Despite the encouraging finding that CD34+ hematopoietic cells are not infected with HTLV-1 [71], experience with autologous transplantation remains limited to case reports [72, 73]. Allogeneic transplantation has also been reported, however with variable success [74-76]. Early relapses have occurred and may be due to infection of donor lymphocytes with HTLV-1 from residual host cells [74].

Encouraging results have been obtained with the combination of CHOP and interferon alpha with zidovudine antiviral therapy with response rates of 60-70%. If at all possible patients with ATLL should be enrolled in clinical trials [64].

**Recommendation**

Six cycles of CHOP (Appendix B) should be administered at 3 weekly intervals. In addition, patients require 6 intrathecal treatments with methotrexate (12 mg via LP or Ommaya reservoir).

Patients with CSF positive ATLL should be treated with 6 cycles of CHOMP chemotherapy (Appendix B). All patients should receive Septra prophylaxis. Response will be assessed clinically at each cycle and by CT scan after the third cycle. At the completion of the sixth cycle of treatment patients should be completely restaged including bone marrow and lumbar puncture if initially positive. Following the completion of therapy, patients should be considered for interferon α 5-10 million units daily in combination with zidovudine 200 mg po five times per day. Patients who progress on therapy or fail to achieve a 50% reduction in disease bulk should be considered refractory and considered for salvage chemotherapy.

### Aggressive NK-Cell Leukemia

**Introduction**

NK-cell leukemia is a very rare disorder, more prevalent in young adults of Asian and Caucasian descent. Patients typically present with systemic symptoms, cytopenias, and organ infiltration especially hepatosplenomegaly. There may only be minimal disease in the peripheral blood and bone marrow at initial presentation. Patients may experience complications such as coagulopathies, evidence of hemophagocytic syndrome, and multi-organ failure. There is significant clinical and pathologic overlap with the NK/T-cell lymphoma subtype [77].

**Baseline Investigations – see page 5**

**Diagnosis**

The leukemic cells are slightly larger than typical granular lymphs with irregular nuclei, prominent nucleoli, and abundant pale cytoplasm. Tissue examination typically reveals massive infiltration with monotonous medium sized cells with evidence of necrosis and hemophagocytosis. The bone marrow is variably involved. The immunophenotype is typically CD2+, CD56+, CD3-, CD57-, CD11+/-, CD16+-/. T-cell receptor genes are in germline configuration, and evidence of EBV activity is invariably present [6, 77].

**Prognosis**

Most patients experience a rapid fulminant course with invariably fatal outcome, often within a few weeks of presentation [6, 77].
Treatment

Aggressive lymphoma type protocols have been attempted, but are often limited by organ failure. The response to therapy is typically dismal. Until further regimens are developed patients with aggressive NK-cell leukemia should be treated according to the guidelines for Diffuse Large B-Cell Lymphoma.

T-Cell Prolymphocytic Leukemia

Introduction

T-PLL is an aggressive T-cell leukemia involving blood, marrow, spleen, nodes, and extranodal structures, especially skin. It is a rare disorder, comprising only 2% of all small lymphocytic leukemias in adults [78].

Baseline Investigations

The following investigations are indicated for most patients with T-PLL at diagnosis:

- CBC, differential, blood film
- Immunophenotyping of peripheral blood lymphocytes
- Serum electrolytes and creatinine
- Liver function tests
- Serum LDH
- Serum uric acid
- Chest x-ray
- Abdominal ultrasound

Neither a lymph node biopsy nor a bone marrow biopsy is required in order to make the diagnosis of T-PLL, however they may be helpful if there is a diagnostic dilemma.

HIV serology, cardiac assessment and gallium scans (see page 5)

Diagnosis

The diagnosis is made by examination of peripheral blood. T-PLL cells are typically medium sized, with basophilic cytoplasm, large round or oval nuclei, and large visible often central nucleolus, however small cell and cerebriform variants are also described. The bone marrow is typically diffusely involved with similar cells. T-PLL cells are immunophenotypically CD2+, CD3+, CD7+, CD4+/-, CD8/-+. T-cell receptor γ and β genes are clonally rearranged [78]. Common chromosomal abnormalities include inversion of chromosome 14 at q11 and q32 (80%), abnormalities of chromosome 8 and deletion of 11q23 [6].

Prognosis

T-PLL is an aggressive leukemia with median survival of less than one year, and typically becomes quickly resistant to standard lymphoma therapies.
Treatment

Combination chemotherapy such as CHOP and nucleoside analogues such as pentostatin have been tried with variable success [79]. Recently encouraging results have been obtained with the monoclonal anti CD52 antibody Campath-1H. An overall response rate of 76% with a complete response rate of 60% was achieve in 39 patients with previously treated T-PLL with evidence of prolonged survival in patients achieving a CR [80]. Autologous and allogeneic transplantation should be considered in appropriate patients who are able to achieve a durable remission.

T-Cell Large Granular Lymphocytic Leukemia

Introduction

T-LGL represents 2-3% of small cell lymphocytic leukemia. Peripheral blood, bone marrow, liver and spleen are typically involved. Patients tend to be younger, with median age of 55 and are often asymptomatic at presentation and have very indolent disease progression. Clinically patients encounter complications of autoimmune disorders such as immune thrombocytopenia, autoimmune hemolytic anemia, aplastic anemia, pure red cell aplasia and neutropenia. Rheumatoid serology is often positive, as well as a polyclonal increase in IgG [81].

Baseline Investigations

The following investigations are indicated for most patients with T-LGL at diagnosis:

- CBC, differential, blood film
- Immunophenotyping of peripheral blood lymphocytes
- Serum electrolytes and creatinine
- Liver function tests
- LDH
- Serum uric acid
- Serum protein electrophoresis
- Direct antiglobulin test
- RF, ANA
- Chest x-ray
- Abdominal ultrasound

Bone marrow biopsy is not required in order to make the diagnosis of T-LGL.

HIV Serology

T-LGL is not associated with HIV infection therefore testing should be limited to patients at risk.

Gallium Scans

Gallium scans are not routinely recommended in patients with T-LCL.

Cardiac Assessment

Cardiac assessment is not necessary at diagnosis, as anthracycline therapy is not indicated in this disorder.
Diagnosis

T-LGL cells are typically larger than normal lymphocytes, with abundant pale cytoplasm and coarse azurophilic granules. Typically LGL cells greater than 2x10^9/L are consistent with the diagnosis. The immunophenotype is typically CD3+, CD4-, CD8+, and CD57+/-. Rearrangements of T cell αβ receptor genes are typically present. There is debate whether T-LGL is a leukemic disorder at all, or rather a reactive lymphocytosis to the underlying autoimmune process, despite the fact that clonality is often demonstrated [6, 81].

Prognosis

The prognosis of T-LGL is excellent with a median survival greater than 10 years. Morbidity is encountered from the autoimmune complications, especially if there is persistent neutropenia. Rare cases have been documented of transformations to more aggressive lymphomas [6, 81].

Treatment

Treatment is directed at the autoimmune complications. Prednisone, methotrexate, cyclosporine, cyclophosphamide and azathioprine have all been used with success [81]. We would suggest prednisone 1 mg/kg as a first-line agent with methotrexate or cyclosporin added as steroid sparing agents.

References