4  CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

A. Management strategy

Chronic lymphocytic leukaemia (CLL) is a disease in which most currently available treatments are designed to alleviate symptoms rather than to cure. Patients with early disease (Binet non-progressive stage A) have a very long survival and should not be treated unless or until there is disease progression. Those with Binet stage B or C disease or progressive stage A should be treated.

Patients, where possible, should be entered into the current NCRN trial. However, patients under the age of 50 with an HLA-identical sibling should be considered for an allograft.

Further information can be obtained from:

B. Diagnostic investigations

- FBC and film (lymphocyte count > 5x10^9/l)
- Lymphocyte morphology ( % prolymphocytes)
- Immunophenotype: see table below (BSH guidelines, 2004)

Table 1 Scoring system for the diagnosis of chronic lymphocytic leukaemia (CLL)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Score points</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>SmIg</td>
<td>Weak</td>
<td>Strong</td>
<td></td>
</tr>
<tr>
<td>CD5</td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>CD23</td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>FMC7</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>CD22 or CD79b</td>
<td>Weak</td>
<td>Strong</td>
<td></td>
</tr>
</tbody>
</table>

Scores in CLL are usually >3, in other B-cell malignancies the scores are usually <3

Additional investigations

These may be helpful at presentation or during course of disease;

- Direct antiglobulin test (DAT)
• Reticulocyte count
• U+E, LFTs, urate
• Serum immunoglobulins and electrophoresis
• CXR, CT or US scan
• Bone marrow aspirate and trephine biopsy – not essential for diagnosis helpful where CLL score low, determining the cause of cytopenias, prognostic information, and assessing response to therapy.
• Cytogenetic/FISH analysis – important to identify high risk, ie p53 deleted patients
• Mutational status of IgV<sub>H</sub>, expression of ZAP-70 or CD38

C. Staging

Rai staging
0  Lymphocytosis only
I  Lymphadenopathy
II  Hepato- or splenomegaly +/- lymphadenopathy
III  Hb <11.0g/dl
IV  Platelets <100x10<sup>9</sup>/l

Binet staging
A  <3 lymphoid areas*
B  ≥3 lymphoid areas*
C  Hb <10g/dl or platelets <100x10<sup>9</sup>/l

*The five possible lymphoid areas comprise: unilateral or bilateral cervical, axillary and inguinal lymphadenopathy, hepatomegaly and splenomegaly

Secondary causes of anaemia (autoimmune or haematinic deficiency) must be identified and treated before staging.

Binet Stage A progressive

Characterised by at least one of the following:
• A persistent rise in the lymphocyte count with doubling time <6 months (according to most recent BCSH Guidelines).
• A downward trend in the Hb and/or platelets.
• At least a 50% increase in the size of the liver and/or spleen and/or lymph nodes. Appearance of lymphadenopathy, hepatomegaly or splenomegaly if not previously present.
• Constitutional symptoms attributable to the disease, e.g. pyrexia, night sweats, weight loss; once other causes have been excluded.
D. Recognised poor prognostic factors include:

- Advanced stage
- Lymphocyte doubling time <12 months
- Diffuse pattern of marrow involvement
- Raised beta2 microglobulin, LDH, soluble CD23
- Unmutated IgVH gene
- CD 38 expression >20-30%
- ZAP-70 expression
- Cytogenetic/FISH abnormalities; 11q deletions, 17p abnormalities (these are all much more easily detected by FISH than conventional cytogenetics). Monoallelic 13q abnormalities confer a better than average prognosis.

E. Indications for treatment

- Progressive marrow failure
- Massive or progressive lymphadenopathy
- Massive or progressive splenomagaly
- Progressive lymphocytosis > 50% increase in 2 months or doubling time <12 months
- Systemic “B” symptoms (exclude other causes)
- Autoimmune cytopenias (refractory)

Patients with early disease (Binet non-progressive stage A) have a very long survival and should not be treated unless or until there is disease progression. Those with Binet stage B or C disease or progressive stage A should be treated.
F. Criteria for measuring response to treatment

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodes</td>
<td>None</td>
<td>&gt;50% decrease</td>
<td>&gt;50% increase, or new</td>
</tr>
<tr>
<td>Liver/spleen</td>
<td>Impalpable</td>
<td>&gt;50% decrease</td>
<td>&gt;50% increase</td>
</tr>
<tr>
<td>Hb (Untrasfsd)</td>
<td>&gt;11g/dl</td>
<td>&gt;11g/dl or 50% up</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>&gt;1.5x10⁹/l</td>
<td>&gt;1.5x10⁹/l or 50% up</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>&lt;4.0x10⁹/l</td>
<td>&gt;50% decrease</td>
<td>&gt;50% increase</td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt;100x10⁹/l</td>
<td>&gt;100x10⁹/l or 50% up</td>
<td></td>
</tr>
<tr>
<td>Aspirate</td>
<td>&lt;30% lymphs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trephine</td>
<td>No interstitial or nodular infiltrate</td>
<td>May be residual nodules</td>
<td></td>
</tr>
</tbody>
</table>

G. Treatment

**General considerations**

- Pre-treatment of Binet stage C patients - (Hb <10g/dl and/or platelets 100x10⁹/l not due to autoimmune phenomena):
  Can give prednisolone 30mg/m² daily for 3 weeks, plus 1 week tailing off, followed 1 or 2 weeks later by the chosen chemotherapy.

- Autoimmune haemolytic anaemia/thrombocytopenia

AIHA and ITP may be triggered, not only by fludarabine, but also by other agents such as chlorambucil. Therefore patients with a positive DAT must be monitored closely throughout treatment.
Immune cytopenias triggered by fludarabine is a contraindication to further fludarabine treatment.

Patients haemolysing before treatment should be treated with prednisolone 1mg/kg (as per ITP guidelines) before initiating chemotherapy. If haemolysis is mild use 2 to 3 weeks of steroids.

- Antibiotic prophylaxis for fludarabine-containing regimen: Co-trimoxazole po 480mg twice a day, 3 days a week (eg Monday, Wednesday, Friday), 960mg once daily 3 days a week or 480mg daily 7 days a week depending on local antibiotic protocols. Start with the first course and continue for at least 6 months after treatment is discontinued. Nebulised pentamidine may be used as an alternative.

- Intravenous immunoglobulin (IVIG) - consider for patients with hypogammaglobulinaemia and recurrent infections. (as per DoH guidelines)

- Treatment option for patients with 17p deletions include: high-dose methylprednisolone and alemtuzumab

**Pre-treatment Evaluation**

- Document histological sub-type of lymphoproliferative disorder according to WHO Classification.
- Document FBC (with film), U&E, creatinine, LFTs, calcium, glucose, serum protein electrophoresis, immunoglobulin levels and a direct antiglobulin test (DAT).
- If staging is relevant this should CT of chest, abdomen & pelvis and bone marrow aspirate & trephine.
- Document height, weight and body surface area.
- Consider ECG ± echocardiogram if clinical suspicion of cardiac dysfunction.
- Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects.
- Obtain written consent from patient or guardian.
- If appropriate, discuss the possibility of pregnancy with female patients of child-bearing age and the need for contraception with both male and female patients.
- If appropriate, discuss potential risk of infertility with patient and relatives.
- Consider intravenous hydration in patients with bulk disease.
• Allopurinol should be given for the first 2 cycles of chemotherapy. 300mg od PO (reduce to 100mg in renal impairment)
• Significant pleural effusions or ascites should be drained to a minimum prior to commencement of fludarabine.

If fludarabine or alemtuzumab to be used, issue patient with DoH irradiated blood information sheet and card: all cellular blood components should be irradiated to prevent the rare occurrence of transfusion associated graft versus host disease.

**Treatment protocols**

2.01 Chlorambucil

2.05 Fludarabine

2.06 Fludarabine & Cyclophosphamide

4.11 R-FC

4.01 FMD

4.02 COP

4.03 Cladribine

4.04 HD Methylprednisolone

4.05 Campath (alemtuzumab)

4.06 Sub-Cut Alemtuzumab
References


Written by: Dr G Abrahamson, Dr S Wagner, Pauline McCalla
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