An overview of CLL care and treatment

Dr Dean Smith
Haematology Consultant
City Hospital
Nottingham
What is CLL?

CLL (Chronic Lymphocytic Leukaemia) is a type of cancer in which the bone marrow makes too many B lymphocytes (white blood cells).
Who gets CLL?

• Commonest adult leukaemia

• Over 3000 diagnosed with CLL in UK each year
  • Estimated 30,000 people in UK living with CLL

• Average age at diagnosis 72
  • Only 1 in 10 under age of 55 at diagnosis

• More common in men than women

• 4 x more likely if family member has it
  • BUT – still low risk and most people who have a relative with CLL do not develop it
  • NOT hereditary
How do patients present?

- Incidental finding

- Systemic symptoms
  - Lethargy, fever, weight loss, night sweats

- Reduced bone marrow function
  - Anaemia (tired, short of breath), bruising/bleeding, infection

- Enlarged lymph nodes and/or spleen and/or liver

- Recurrent infections
  - Viral or bacterial

- Autoimmune manifestations
  - Haemolytic anaemia, immune thrombocytopenia (ITP)
How is CLL Diagnosed

• History and examination

• Full Blood Count
  • Lymphocytosis – lymphocytes >5 for 3 months
  • +/- anaemia and thrombocytopenia (low platelets)

• Blood film
  • Typical appearance of cells down microscope

• Immunophenotyping on peripheral blood

• Lymph node biopsy
  • less commonly required. Can help differentiate CLL from lymphoma
Blood film

- Smear cells
- Lymphocytes, i.e. CLL cells
- Red Blood Cells
Immunophenotyping

- A technique used to study the proteins expressed on cells

Blood cells stained with antibody labelled with fluorescent dye. Each dye binds to a specific protein. Cells then passed through machine which detects the fluorescent dye and therefore tells us which articular protein is on cell surface.

Computer generates graphs which we interpret. CLL cells have a particular pattern.

e.g. CD5 and CD23 positive

e.g. CD5 positive, CD23 negative
Bone marrow and CT

• CT scan – to assess lymphadenopathy, liver and spleen
  • No evidence to support this in asymptomatic patients
  • Routinely done in clinical trials to allow assessment of response to treatment
  • Pre- and post-treatment CT scanning should be considered
  • No evidence for routine surveillance scanning post therapy (affected treatment decision in 2 out of 176 pts)

• Bone marrow biopsy
  • Not essential for diagnosis
  • Determine the cause of cytopenias (low blood counts) prior to treatment
  • Determine the cause of prolonged cytopenias post treatment
  • Required to define “complete response” to treatment
What are the stages of CLL?

<table>
<thead>
<tr>
<th>BINET STAGE</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 3 lymphoid areas</td>
</tr>
<tr>
<td>B</td>
<td>3 or more lymphoid areas</td>
</tr>
<tr>
<td>C</td>
<td>Hb &lt; 100 or platelets &lt; 100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAI STAGE</th>
<th>Risk Group</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Lymphocytosis only</td>
</tr>
<tr>
<td>I</td>
<td>Low</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>II</td>
<td>Intermediate</td>
<td>Enlarged liver or spleen + lymphocytosis</td>
</tr>
<tr>
<td>III / IV</td>
<td>High</td>
<td>Hb &lt; 110 or platelets &lt; 100</td>
</tr>
</tbody>
</table>

The 5 lymphoid areas are neck, axilla, groin, liver, spleen
When should we start treatment?

• May NEVER need treatment

• With conventional treatments, CLL not cured

• No trials have shown benefit for treatment in early stage CLL – “watch and wait”
  • This idea is being re-visited in trials using novel therapies, e.g. Ibrutinib

### Table 2. Recommendations regarding indications for treatment in CLL

<table>
<thead>
<tr>
<th></th>
<th>General practice</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat with Rai stage 0</td>
<td>NGI*</td>
<td>RQ</td>
</tr>
<tr>
<td>Treat with Binet stage A</td>
<td>NGI*</td>
<td>RQ</td>
</tr>
<tr>
<td>Treat with Binet stage B or Rai stage I or Rai stage II</td>
<td>Possible*</td>
<td>Possible*</td>
</tr>
<tr>
<td>Treat with Binet stage C or Rai stage III or Rai stage IV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment of active/progressive disease</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treat without active/progressive disease</td>
<td>NGI</td>
<td>RQ</td>
</tr>
</tbody>
</table>

General practice is defined as the use of accepted treatment options for a patient with CLL who is not enrolled in a clinical trial.

NGI indicates not generally indicated; and RQ, research question.

*Treatment is indicated if the disease is active as defined in section 4.
When should we start treatment?

• Treat active or progressive disease:
  
  • 1. Bone marrow failure (development or worsening of anaemia or low platelets)
  
  • 2. Massive splenomegaly (6cm below ribs) or symptomatic
  
  • 3. Massive (>10cm) or progressive lymphadenopathy
  
  • 4. Rapid increase in lymphocytes (double in < 6 months)
  
  • 5. AIHA or ITP not responding to steroids or other treatment
  
  • 6. Constitutional symptoms:
    • 10% weight loss in <6 months
    • Fever > 38°C for > 2 weeks
    • Unexplained sweat > 4 weeks
    • Extreme fatigue
CLL Is A Heterogeneous Disease

- Many stage A patients on “watch and wait” will have stable blood counts and never require therapy
- Some stage A patients will rapidly progress and require therapy
- Some patients respond very well to therapy and have a prolonged period of remission
- Some patients respond less well to therapy
- Some patients respond very well to therapy but have a “short” period of remission, relapse and require further therapy
Factors Affecting Prognosis in CLL

<table>
<thead>
<tr>
<th>Patient Related</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Performance Status</td>
</tr>
<tr>
<td></td>
<td>Other illnesses</td>
</tr>
</tbody>
</table>

| Treatment Related       | Type of treatment, i.e. how intense|
|                        | Response to treatment              |
|                        | Minimal residual disease status    |

| Disease Related         | Disease stage                       |
|                        | Marrow failure                      |
|                        | Biomarkers                           |
|                        | Lymphocyte doubling time             |

**BIOMARKERS**

FISH (genetic) abnormalities – see next slide

Immunoglobulin heavy chain variable region (IgVH) mutational status (Good prognosis if mutated)

CD38 expression  (Good prognosis if not expressed)
FISH – Fluorescent In Situ Hybridisation

A genetic technique using fluorescent probes that bind to complementary sequences of DNA.

Prognostic FISH Markers In CLL

Good prognosis: Loss part of chromosome 13

Less good: Loss of part of chromosome 17 or 11

CLL cell showing 17p deletion
An example of the heterogeneity between patients

FCR regimen remains current gold standard treatment for young fit patients.

As years go by, will some of these patients never need any further treatment? There is much variation between patient subgroups in terms of response.

Progression Free Survival also shorter if stage C rather than stage B, i.e. multiple factors influencing response to treatment.
Idelalisib + Rituximab As Frontline Treatment For CLL

For patients with TP53 (or 17p) deletion, Idelalisib would be preferable to FCR.

Thus, we are tailoring therapy to each patient's individual needs.
How do we decide what treatment to offer?

- Patient related factors
  - Age
  - Co-morbidity, e.g. renal function
  - Patient wishes, e.g. tablet vs infusion

- Disease related factors
  - e.g. genetics

- Response to prior therapy
  - How long a remission? (e.g. 3 yr cut off FCR)
  - How was therapy tolerated?

- Aiming for personalised therapy
Treatment Options If No Prior Treatment

**Watch and wait**

**Chlorambucil**

**Chlorambucil + Monoclonal Antibody***

**Bendamustine + Rituximab**

**Fludarabine + Cyclophosphamide + Rituximab**

More intensive

* Ofatumumab or Obinotumumab

**Bone Marrow Transplant**
Monoclonal Antibodies

Monoclonal antibodies are made in a laboratory to mimic antibodies that our own immune system produces in response to bacteria.

Monoclonal means all one type.

They are designed to recognise and attach to specific proteins on the surface of CLL cells.

In doing so, this leads to cell death.

Specifically targeting the CLL cells leads to less side effects than conventional chemotherapy.
Treatment Options If Prior Treatment

**Watch and wait**

**Chlorambucil**

**Chlorambucil + (Monoclonal Antibody)**

**Bendamustine + Rituximab**

**Idelalisib + Rituximab**

**Fludarabine + Cyclophosphamide + Rituximab**

**Ibrutinib**

**More intensive**
Response To Treatment

• Measure response by fixed criteria
  • e.g. partial response if lymphocytes, lymph node size and amount of CLL in bone marrow reduced by 50%
  • If all above back to normal, complete response

• The better a patient responds, the longer the remission, i.e. a patient with a complete response likely to remain in remission longer than a patient with partial response.

Ideally, we aim to kill as many CLL cells as possible

This is why we generally continue with treatment even if blood counts and lymph nodes are normal after 2 or 3 cycles, to any few remaining cells in the bone marrow.

Aiming for “Minimal Residual Disease”
Infection and CLL

• CLL – a malignancy of the B cells, i.e. cells of immune system which make antibodies

• CLL cells are abnormal B cells. As such, immune system is suppressed and patients more susceptible to infection

• Partly due to a decrease in antibody secretion (something we can measure on blood tests)

• Partly due to impact on other cells in immune system – harder to quantify

• Patients with CLL therefore at risk of bacterial infection and viral infection
Infection and CLL

• Treatment for CLL depletes the immune system further

• Chemotherapy aimed to kill the CLL cells. Also kills some of the “good” cells in immune system

• Can take many months for immune system to recover post treatment

• Risk of reactivation of viruses, e.g. herpes simplex (cold sore) and varicella zoster (shingles)
Supportive Treatments

• Antibiotics and antivirals
  • Aciclovir – to prevent cold sores and shingles
  • Co-trimoxazole – to prevent chest infection PCP (Pneumocystis carinii pneumonia)
  • Other antibiotics – depending on site of recurrent infections, e.g. Azithromycin

• Immunoglobulin Replacement Therapy
  • A transfusion of general immune antibodies prepared from blood donation
  • Given if patient immunoglobulins are low and recurrent infections despite antibiotics

• Red cell and platelet transfusions
Summary

• We have an increasing understanding of genetics and molecular tests in CLL which give information about outcome (i.e. prognosis) and likelihood of response to a particular treatment (i.e. predictive)

• Each patient with CLL will have their own individual disease and treatment course

• Increasingly in the future, we will be able to tailor therapy to the individual

• A number of novel therapies now available