Chronic Lymphocytic Leukaemia

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Chronic Lymphocytic Leukaemia

- Commonest leukaemia in western world
- Incidence of 4/100,000 pa
- Familial risk (7-8 fold)
- Median Age 72 years
- M:F = 2:1
- Diagnosis is usually made as an incidental finding on a routine FBC
- Highly variable natural history
  - Clinical and genetic heterogeneity
  - Prognostic markers (IGVH, TP53)
Case History

- A 78 year old man
- Fit and well
- Routine monitoring for PSA
- FBC also taken
- Noted to have a raised WBC $11 \times 10^9$/l
- Lymphocytes $6 \times 10^9$/l (normal range 1-3)
- Report states- “smear cells seen on film? CLL”
What would you do?

A. Ignore the result
B. Repeat the FBC in a year when the PSA is next due
C. Repeat the FBC in 3 months
D. Refer for a standard haematology specialist appointment
E. Tell the patient they may have leukaemia and refer on an urgent two-week-wait rule with suspected malignancy
F. Phone/write to the Haematologist for advice
Chronic Lymphocytic Leukaemia

- Most patients are asymptomatic at the time of diagnosis
- Clinical features
  - Immune dysfunction
    - Infection
    - Autoimmunity (affecting components of blood)
  - Tissue infiltration
    - Lymph nodes, spleen & other tissues
    - Eventual BM failure (cytopenia)
Case History

• A 52 year old woman
• Mild fatigue, no other B symptoms (fevers, sweats, weight loss)
• No recent infections or dental problems
• Cervical lymph nodes present for 2 months – about 1-1.5 cm, painless, mobile
• No other palpable disease or signs of local infection
What would you do?

A. Ask her to return in a month if the nodes have not gone
B. Check viral screen
C. Check a FBC
D. Send a TWW referral to the head and neck team
E. All of B-D
F. None of the above
Case History

• The patient was sent to the head and neck surgeons
• Lymph node biopsy reported as Small Lymphocytic Lymphoma
• Referred for full TAP CT which showed generalised low-volume lymphadenopathy (<1.5 cm)
• Referred to haematology
• Had a FBC – lymphocyte count of 35, otherwise normal
• Flow cytometry confirmed CLL !!
Chronic Lymphocytic Leukaemia

- CLL and SLL are the same disease. About 10% patients may present with lymphadenopathy alone with normal FBC (BM usually involved)
- About $\frac{1}{3}$rd patients with CLL may never require any treatment
- Infection is a risk even in patients with untreated CLL
- Progression is associated with increased tumour bulk and genetic complexity
- Treatment requirement is based on a set of criteria confirming disease activity/progression
- Natural History- remissions /relapses over years-decades
- Incurable (but often manageable) with current therapy
A 52 year old man with untreated CLL presents with a painful rash on his right chest wall
What would you do?

A. Send him home
B. Send him to A&E
C. Phone his haematology team
D. Prescribe topical aciclovir cream
E. Prescribe oral aciclovir
F. Administer the zoster vaccine
Infectious complications in CLL

- Common: 0.26- 0.47 per patient year
- Mainly bacterial respiratory tract (S pneumonia, S aureus, H influenzae)
- Chronic sinusitis and bronchiectasis
- Herpes virus re-activation (shingles)
- Fungal and opportunistic infections rare in untreated patients
- Infection is major cause of morbidity and mortality (50%) in advanced CLL
Early-Stage CLL: Watch & Wait Remains the Standard Approach

**French Binet-A Trial**

- Custom image showing survival curves for Chlorambucil and No Therapy with a p-value of 0.23.

**French-German CLL7 Trial**

- Custom image showing survival curves for Low risk: W&W, High risk: FCR, and High risk: W&W.

Schweighofer et al. ASH 2013

Patients on W&W should be encouraged to follow a normal healthy lifestyle.
The evolution of treatment options in CLL

1960-70s
- Alkylating agents
  - chlorambucil
  - cyclophosphamide

1980s
- Purine analogs
  - fludarabine
  - pentostatin
  - cladribine

1990s
- Purine analogs + alkylators
  - FC
  - PC

2000s
- Chemo-immunotherapy
  - bendamustine*

2010s
- Novel therapies
  - .......chemo-free!

Significant improvements in CR and ORR rates

bendamustine*

Until this century no significant change in the natural history of CLL
Tailoring treatment for CLL patients

Many factors must be considered in order to optimise management in patients with CLL

- **Disease evaluation** (Stage, prognostic/predictive markers - TP53)
- **Comorbidities and vital organ status**
- **Toxicity**
- **Age**
- **Supportive care**
- **Life expectancy**
- **Quality of life**
- **Medical fitness (CIRS)**
- **Patient preference (administration)**

What is the personalised goal of treatment?

CIRS, Cumulative Illness Rating Scale
Tailoring First-Line therapy for patients with CLL: what are the challenges?

A. Patient assessment
B. Defining treatment goals
C. Selection of appropriate therapy
D. Improving remissions and survival
E. Improving quality of life
Challenge 1: Patient Assessment
Assessing co-morbidity

<table>
<thead>
<tr>
<th>Single assessments</th>
<th>Combined assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity scores</td>
<td>Nutrition scores</td>
</tr>
<tr>
<td>Locomotion scores</td>
<td>Ability scores</td>
</tr>
<tr>
<td>Cognition scores</td>
<td></td>
</tr>
</tbody>
</table>
CLL patients are older and most have some co-morbidity

Median Age at diagnosis 72 years
Co-morbidity and outcome

- All cause mortality increased in co-morbid patients
- **However**, CLL related deaths major determinant of lower OS
- Maintenance of dose intensity is a problem
- **Key issue is being able to deliver safe and effective therapy in this group of patients**

Challenge 2: Defining Treatment Goals

- Life expectancy in the UK has improved
- Patients with CLL still have reduced survival compared with the general population
- Good remissions can be achieved with therapy and result in longer survival
- Longer remission is associated with improved quality of life
- Simple palliation/symptom control is not appropriate for most patients with CLL
Challenge 3: Selection of appropriate therapy

Hypertension
Creatinine clearance < 50ml

SLOW-GO  NOT–SO-GO-GO  GO-GO
The Go-Go patient
FCR is the ‘gold standard’\textsuperscript{1}

\textbf{Med. PFS (6yr FU)}\textsuperscript{*}
- FCR: 57 months\textsuperscript{*}
- FC: 33 months\textsuperscript{*}

Overall survival
- FCR (n=408)
- FC (n=409)

Main toxicities: neutropenia and infection

A 65 year old woman who has recently been treated for CLL presents with a dry cough and SOB, chest sounds clear. Do you:

A. Send her to A&E
B. Call her specialist team
C. Conclude that this is likely viral and send her home
D. Give a course of antibiotics
Opportunistic Infections in CLL

- Particularly related to treatment (steroids, purine analogues, alemtuzumab, idelalisib)
- Increased risk in heavily pre-treated patients
- A good response to CLL therapy may reduce infection risk
- Listeria monocytogenes, pneumocystis jerovcii, nocardia, mycobacteria, fungal
- Viral reactivation (herpes, CMV, EBV, Hepatitis B&C)
- Respiratory viruses (Para Flu, RSV)
- PML (JC virus)

*PJP Pneumonia*
Mr AW 65 y man with heavily pretreated fludarabine-refractory CLL treated with CamPred and achieved a good PR. Presented 3 months after completing treatment with blurred vision in one eye. Otherwise asymptomatic.

Ophthalmology review revealed mass. Biopsy showed aspergillus. MRI revealed small fungal lesion. Treated with voriconazole as OP and all completely resolved.
The Not-So-Go-Go patient

CLL10 Study: FCR vs BR in front-line

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (% of pt)</th>
<th>BR (% of pt)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>90.8</td>
<td>78.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematological AEs</td>
<td>90.0</td>
<td>66.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>81.7</td>
<td>56.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>79.6</td>
<td>47.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>12.9</td>
<td>9.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.5</td>
<td>14.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Infection</td>
<td>39.0</td>
<td>25.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- Improved PFS with FCR
- Less toxicity with BR

The Slow-Go Patient: Adding Targeted treatment CLL11 and Complement 1

- Reflected this group of patients well:
  - Median age 72 y,
  - Median CIRS score 8
  - 2/3 patients creatinine clearance < 70
- Both studies confirm that addition of a CD20 monoclonal antibody improves efficacy - PFS
  - Chlorambucil: 11-13 m
  - R-chlorambucil: 16.3m
  - G-chlorambucil: 31.1m
  - O-chlorambucil: 22.4m
- Comparable toxicity
- MRD neg remissions achieved in a proportion

Obinutuzumab + Clb prolonged median TTNT by more than one year compared to R-chlorambucil and by 3 years compared to chlorambucil alone.
Mr M: DOB 1936

- Referred from prostate team, aged 74y in 2010 with mild lymphocytosis and thrombocytopenia
- Asymptomatic
- Prostate cancer diagnosed 2003, IMRT 2004 hormone treatment until 2006
- No other co-morbidities
- BBC TV documentary producer
Mr M: DOB 1936

- No palpable disease
- FBC: Hb 141, WBC 10.1 (L 6.7) platelets 131
- Diagnosed Stage A CLL
- Watch and wait
- 2013 developed DVT and PE following long haul flight, anticoagulated
- Slow steady disease progression- splenomegaly, LN, falling Hb and platelets
- 2014 Wife had acute diagnosis of DLBCL, successfully treated
- Developed mild intra-cerebral bleed following a fall 2015
Mr M: DOB 1936

- By Sept 2015 Hb 95, WBC 80, Platelets 57
- Commenced Chlorambucil + obinutuzumab (NICE approved)
- WBC fell from 80 to 45 after 1st dose and to 1.2 (neutrophils 1) at day 8
- Initial Infusion reaction but no other AEs
- Completed 6 cycles Feb 2016- No palpable disease; Hb 131, WBC 8.3 (N7), platelets 128
- Re-staging investigations (CT and BM) showed CR
## Challenge 3: Selection of Appropriate Therapy

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit GO-GO</td>
<td>FCR</td>
</tr>
<tr>
<td>Intermediate NOT-SO-GO-GO (older age, renal function)</td>
<td>BR</td>
</tr>
<tr>
<td>Older less fit SLOW-GO</td>
<td>Chlorambucil+ Obinutuzumab</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil+ ofatumumab</td>
</tr>
<tr>
<td>TP53 del/mutation</td>
<td>Alemtuzumab+ steroids</td>
</tr>
<tr>
<td></td>
<td>Idelalisib+ Rituximab</td>
</tr>
<tr>
<td></td>
<td>Ibrutinib</td>
</tr>
<tr>
<td>All patients</td>
<td>Available Clinical Trial</td>
</tr>
</tbody>
</table>
Challenge 4: Improving Survival

FC vs FCR

Chlorambucil alone vs + GA101 or R

Addition of an Anti-CD20 monoclonal antibody to conventional chemotherapy backbone improves survival for GO-GO and SLOW-GO patients
Challenge 5: Improving quality of life (QoL)

- Most patients requiring treatment report impaired QoL (fatigue, reduced physical, role and social function)

Global QoL: Percentage improved by Quality and Duration of Response to Treatment

- Patients who respond to therapy have improved QoL compared to baseline and compared to those who do not respond.
- Patients who remain in remission have better QoL than those who have progressed.
- Therefore achieving a remission and remaining in remission is associated with the greatest QoL improvement.
CLL: Conclusions

• Most patients are diagnosed on a routine FBC when they are otherwise well
• Some patients will present with lymph node enlargement, but the diagnosis can often be made from PB without need for biopsy
• A significant proportion of patients will never require treatment and others not for years or even decades
• Treatment is carefully tailored and based on numerous personal (age and co-morbidity) and disease-related factors
• Treatment is very effective at achieving durable remissions in the majority of patients, even older less fit individuals, and delivering a good quality of life
• Many new therapies ("just need to stay one drug ahead of your disease" !)
• The major complication of the disease and the therapy is INFECTION