Executive Summary

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the Western world, but is significantly less frequent in Asia. The median age of diagnosis in the USA, Europe and Australia is approximately 70 years of age, with about one quarter of patients aged <65 years and approximately 6% less than 50 years [1, 2]. CLL has a male predominance, and males are more likely to have disease progression and require therapy. The disease is highly heterogeneous: patients with indolent disease may never require therapy while others can progress rapidly and require therapy shortly after presentation. The most common presentation in developed countries is an asymptomatic lymphocytosis detected by incidental blood tests. Patients with progressive disease have a rising lymphocytosis, adenopathy, hepatosplenomegaly and bone marrow infiltration resulting in bone marrow failure with anaemia and thrombocytopenia [1]. These clinical findings are the basis for the two principal staging systems of Rai and Binet [3, 4].

Only patients with progressive disease require therapy. The proportion of patients who never require therapy varies from ~50% with a community referral base to very few in tertiary referral institutions. Common complications of CLL are hypogammaglobulinaemia and infection [5], autoimmune haemolysis and thrombocytopenia [6] and progression to high-grade lymphoma (“Richter transformation”) [7, 8].

CLL therapy has undergone momentous changes over the last few decades. The first major change was the evolution from single alkylator based therapy to immunochemotherapy. The second major change now in progress is the introduction of small molecular inhibitors of the B-cell receptor signaling and other key biological survival and apoptotic pathways. Previously, the oral alkylator chlorambucil (Cbl) was the basis of therapy. During the 1990s to 2000s, Keating and colleagues at the MD Anderson pioneered the use of fludarabine, initially as a single agent, then in combination with cyclophosphamide (FC) and finally with the addition of rituximab (FCR) [9-12]. A large randomized clinical trial, the UK LRF CLL4 Study initially documented that fludarabine plus cyclophosphamide (FC) was superior to fludarabine or chlorambucil as single agents with progression free survival (PFS) respectively of 43, 23 and 20 months [13]. Subsequently the large randomized CLL8 trial showed the additional of rituximab to FC (FCR) was superior and hence combination immunochemotherapy with FCR is now the standard of care for younger, fit patients resulting in 90% overall response rate and 44% complete remission rate [14], and an overall survival benefit compared to FCR. Progression free survival (PFS) following FCR is 52 months compared to PFS of ~11-20 months with Cbl alone. This UK LRF CLL4 Study began with using the FC combination intravenously over 3 days. This 3 day intravenous schedule was adopted by the CLL8 Study. During the course of UK LRF CLL4, an orally administered schedule was introduced which administered the same drugs over 5 days.
rather than 3 days [13]. An Australian study focused on fit patients aged 65 years and over also adopted this 5 day oral regimen as the method of administration [15].

More recently combination therapy with bendamustine/rituximab has been shown to be highly effective in CLL and should be considered one of the standard regimens offered to patients. In the German Chronic Lymphocytic Leukemia Study Group, it was demonstrated that 90.5% of patients were alive at 27 months, and the median event-free survival was 33.9 months.[26]

For patients with comorbidities or unable to tolerate one of the regimens above, Cbl with the novel CD20 antibody obinutuzumab has been documented as superior to Cbl with rituximab which in turn is superior to Cbl alone in the large CLL11 study[16].

There has been substantial progress documenting the genetic basis for the heterogeneity of CLL, particularly with lesions in the TP53 and ATM genes on chromosomes 17 and 11, respectively, which predict poorer survival[17]. The mutational status of the immunoglobulin heavy chain variable gene (IGHV) is another factor, as are mutations in Notch1, SF3B1 and others. Recently, inhibitors of the B-cell receptor (BCR) signal pathway (ibrutinib and idelalisib) and bcl-2 (Abt-199) have shown exceptionally promising results in patients with TP53 defects and those with relapsed and refractory disease, leading to the recent FDA approval of the 2 BCR inhibitors in the U.S.. These agents remain in active trials and under investigation. These tests and agents are not currently widely available and therefore the agents are not recommended at this time to be added to the EML.

**Public Health Relevance**

GLOBOCAN estimates worldwide incidence of overall leukemia in 2012 to be 351,965 cases (ASR of 4.7 per 100,000). The incidence of overall leukemia in more developed regions in 2012 was estimated as 141,274 (ASR of 7.2 per 100,000) versus an incidence of 210,691 (3.8 per 100,000 person-years) in less developed regions (22). GLOBOCAN does not provide specific information about chronic lymphocytic leukemia (CLL).

According to a German study published in 2011, CLL is the most common form of leukemia in the Western hemisphere; it accounts for approximately one-third of new cases of leukemia (23). A US study published in 2004 estimates the worldwide incidence of CLL to be between < 1 and 5.5 per 100,000 people (24) The highest incidence rates in 2004 were found to be in Australia, US, Ireland and Italy. The US study proposes that CLL is more common in adult males than in females and that CLL presents in Caucasians more often than in Blacks. According to the same study, the median age of diagnosis is between 64 to 70 years, while the German study estimates median age of diagnosis to be between 70 to 72 years. In the US in 2004, five-year survival rate was 83% for those < 65 years old and 68% for those 65 years old and older. Family history of CLL is a noted risk factor for developing the disease (25).
Requirements for diagnosis, treatment, and monitoring

**Diagnostics:**
A full blood count with morphological examination of the peripheral blood film is essential. An immunophenotype of CD20, CD19, and CD5 positivity (usually also with CD23 positivity) to document the characteristic CLL phenotype by flow cytometry, is also required to differentiate CLL from other lymphoproliferative disorders. A bone marrow is only performed to assess marrow reserves and genetic analysis prior to therapy, and after treatment completion to assess response. After initial therapy, patients in remission but with detectable minimal residual disease by flow cytometry in marrow or blood predicts earlier relapse and shorter progression free and overall survival. Flow cytometry requires a significant skill set and training.

**Testing:**
Regular full blood counts are essential during the course of therapy to monitor response and evaluate potential treatment related toxicity such as anaemia, neutropenia and thrombocytopenia. Autoimmune haemolytic anaemia (AIHA) occurs in ~15% of patients with CLL and the direct antiglobulin test (DAT), together with biochemical analysis for bilirubin and lactate dehydrogenase (LDH) are important to diagnose and monitor this complication. A bone marrow examination is important for pre-treatment evaluation and for response assessment [18]. Flow cytometric evaluation is also important.

Where available fluorescence in-situ hybridization, or karyotypic analysis are essential to detect the common adverse genetic abnormalities (11q- and 17p-), but add significant cost. Testing for IGHV mutational status and molecular mutations is not currently routine practice in most clinical environments. Criteria for assessment of response have been published in the International Workshop of CLL[18].

**Administration and Care of Patients:**
Administration requires intravenous infusion capacity for the rituximab, and requires that the patient have regular access to clinical care. The fludarabine and cyclophosphamide may be given intravenously or orally. In developed countries rituximab administration is usually performed in outpatient facilities, though in other settings, patients may be treated in in-patient facilities. Rituximab can cause severe allergic reactions and must be given slowly, with pre-medications including steroids and anti-histamines as well as close monitoring and additional supportive medicines readily available.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including bone marrow suppression, infection, allergic reactions to rituximab, and gastrointestinal toxicity. Social and financial wellbeing can be impacted by treatment side effects and should be monitored and addressed as well.

Patients with CLL should be followed indefinitely in view of the risk of disease relapse and further progression, and potential need for further therapy. A proportion of patients with mutated IGHV genes have been followed for up to 10 years with no recurrence. By contrast, for patients
who progress within 2-3 years after front-line FCR, the long-term outlook was grave until the recent arrival of B-cell receptor pathway inhibitors.

Age, fitness, and overall medical and performance status are critical components of the evaluation of the patient with CLL. For younger fit patients, FCR provides markedly superior outcomes and PFS providing a substantial period of time when patients have a normal quality of life. This allows the individual to continue to work and remain productive, and allows their families to reach maturity resulting in a major social and psychological benefit for the patient, the family, and for society. By contrast, the elderly or infirmed patient may have different treatment goals and the shorter period and less complete degree of disease control achieved with chlorambucil may be appropriate goals. Chlorambucil is already in the List of Essential Medicines, and reviewers recommend it remain on the list for palliative care in CLL patients.

**Overview of Regimens**

The following tables include basic information on administration and dosing for FCR. The FCR regimen may be administered intravenously or orally, but it important to note that the dose and duration of the FC component are different with the intravenous versus oral regimens. The protocol excludes ancillary medications pertaining to the management of side effects such as prophylactic growth factor support to minimize neutropenia, and prophylactic antibiotics and anti-viral therapy for minimization of infection risk.

For the therapeutic regimens considered, the CLL8 study planned 6 cycles of FCR therapy, and the majority of these front-line patients tolerated this treatment. The CLL8 study also documented that twice as many patients achieved a complete response (CR), and also minimal residual disease (MRD) negativity, with 6 cycles compared to 3 cycles of treatment [19]. Generally therefore, 6 cycles of therapy is recommended. However, for patients with recurrent and persistent cytopenia, or other persistent grade 3 or 4 toxicity, early cessation may be important. It is important to note that clearance of CLL cells from the peripheral blood is not evidence of complete remission. The documentation of CR requires a bone marrow biopsy and imaging as outlined in the International Workshop on CLL guidelines.

**Standard Regimens**

**FCR Regimen: planned 6 cycles**

Note difference in duration (dose) with IV vs. oral regimen. These IV and PO regimens are considered approximately dose equivalent.

**Using Intravenous FC over 3 days**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine</td>
<td>IV</td>
<td>25 mg/m²</td>
<td>1-3</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>IV</td>
<td>250 mg/m²</td>
<td>1-3</td>
</tr>
<tr>
<td>Rituximab</td>
<td>IV</td>
<td>375 mg/m²</td>
<td>1, then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg/m²</td>
<td>2-6</td>
</tr>
</tbody>
</table>
Using Oral FC over 5 days

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine</td>
<td>PO</td>
<td>24 mg/m²</td>
<td>1-5</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>PO</td>
<td>150 mg/m²</td>
<td>1-5</td>
</tr>
<tr>
<td>Rituximab</td>
<td>IV</td>
<td>375 mg/m²</td>
<td>Cycle 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg/m²</td>
<td>Cycles 2-6</td>
</tr>
</tbody>
</table>

Standard Bendamustine-Rituximab Regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine</td>
<td>IV</td>
<td>90 mg/m²</td>
<td>1,2</td>
</tr>
<tr>
<td>Rituximab</td>
<td>IV</td>
<td>375 mg/m²</td>
<td>1</td>
</tr>
</tbody>
</table>

B-R administered every 4 wks x 4 cycles

Note – it is recommended that rituximab be used as outline above, but if it is unavailable or unaffordable, these regimens can be used without rituximab. The results are inferior to rituximab containing regimens, but benefit is still substantial

Alternative Regimen for advanced symptomatic disease

R-CVP: q 3 wks, 6 cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>IV</td>
<td>375 mg/m²</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>IV</td>
<td>750 mg/m²</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>IV</td>
<td>1.4 mg/m² (cap dose at 2 mg)</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>PO</td>
<td>100 mg, orally</td>
<td>1-5</td>
</tr>
</tbody>
</table>

(Note – if rituximab not available, give CVP at the same doses)

The FCR regimen universally causes neutropenia. This in turn is commonly treated with growth factor support (G-CSF), which may significantly increase therapy related costs. Please see the additional G-CSF supporting document appended to this proposal.

Assessment of CLL response to therapy requires a bone marrow biopsy and imaging to document response as detailed in the iwCLL guidelines. Clearance of CLL cells from the peripheral blood is not an adequate therapy end-point and does not represent CR.

Supportive Care

Hypogammaglobulinaemia is a common complication of CLL. For patients with reduced IgG, CLL and recurrent episodes of bacterial infection, regular immunoglobulin replacement therapy reduces infection rates and may improve quality of life [20].
Review of Benefits and Harms

Benefits
The FCR regimen gives clearly superior outcomes when administered to relatively fit CLL patients. The PFS with FCR is 57 months compared to chlorambucil which achieves a PFS of ~11-20 months. The time to second therapy is with FCR is ~5-7 years compared to ~2 years with chlorambucil with better quality of life in keeping with the much longer period of excellent disease control with FCR.

Harms and Toxicity Considerations

Common
Rituximab can cause allergic reactions and must be given slowly with pre-medications including steroids and anti-histamines as well as close monitoring and supportive medicines readily available. Reactions are commonly mild following premedication.[11]

Serious
The principal toxicity related to the FCR regimen is myelosuppression and infection, with high rates of severe neutropenia in up to 34-58% of patients and associated infection in 10-25% of patients.[11,12,14] Myelosuppression with this regimen may persist >3 months and commonly requires growth factor support to shorten the duration of neutropenia and reduce risk of infections.[14,21] Thrombocytopenia and anemia also occur, and blood transfusion support is frequently required.

Systematic Reviews
In view of the relatively recent randomized clinical trial (RCT) outcomes and rapid evolution of CLL therapy from single agent alkylating agents (chlorambucil) to fludarabine, then combination FC, and in turn to FCR, no systematic or meta-analyses have been performed. Furthermore, the rapidly changing landscape with the advent of signal pathway inhibitors means that randomized controlled clinical trials will continue to be the principal source of informative data.

Recommendations
The reviewers recommend the incorporation of CLL treatment options into the WHO Model List of Essential Medicines, and recommend specifically that fludarabine, rituximab, and bendamustine be added to the core Essential Medicines List.

Additions proposed for Section 8.2 of the EML

Fludarabine
Rituximab
Bendamustine
CHRONIC LYMPHOCYTIC LEUKEMIA
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

References


