Chronic lymphocytic leukaemia (CLL) – EML

The application sought endorsement of cyclophosphamide, vincristine and prednisone, already listed on the Model List of Essential Medicines, for the treatment of chronic lymphocytic leukaemia (CLL). The application also sought the addition of fludarabine, rituximab and bendamustine to the core list for this indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Chronic lymphocytic leukaemia is the most common form of leukaemia in the developed world, but is significantly less frequent in Asia. The median age of diagnosis in Australia, Europe and USA is approximately 70 years, with about 25% of patients aged under 65 years and approximately 6% under 50 years *(1, 2)*. Male patients predominate and are more likely than females 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 *(3)*. These clinical findings are the basis for the two principal staging systems *(3, 4)*.

Only patients with progressive disease require therapy. The proportion of patients who require therapy varies from approximately 50% with a community referral base to the absolute majority 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 past few decades. The first major change was the evolution from single alkylator-based therapy to immunochemotherapy; the second – now in progress – is the introduction of small molecular inhibitors of B-cell receptor (BCR) signalling and other key biological survival and apoptotic pathways. Previously, the oral alkylator chlorambucil (Cbl) was the basis of therapy. The use of fludarabine was pioneered during the 1990s and 2000s, initially as a single agent, then in combination with cyclophosphamide (FC) and finally with the addition of rituximab (FCR) *(9-12)*.

Other chemotherapy regimens have also been successfully combined with rituximab for treatment of untreated or relapsed patients with CLL: bendamustine in association with rituximab has been shown to be effective and well tolerated in a phase II trial in high risk patients *(13)*, and this regimen has been evaluated in a randomized controlled trial: the

interim analysis shows that FCR might be associated with longer progression-free survival (PFS), but with a significantly higher rate of severe adverse events *(14).*

There has been substantial progress in 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 *(15)*. 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 BCR signal pathway (ibrutinib and idelalisib) and of bcl-2 (Abt-199) have shown promising results in patients with *TP53* defects and those with relapsed and refractory disease, leading to the recent approval of these two BCR inhibitors by the U.S. Food and Drug Administration. Ibrutinib and idelalisib are recommended for use in treatment of adult patients with CLL who have received at least one prior treatment, as well as for first-line treatment of patients with a specific genetic mutation that makes them unsuitable for chemoimmunotherapy. Trials of these medicines as first-line therapy are now underway; however, because they are not currently widely available and their use has been confined to trials, these agents are not proposed for addition to the EML at this time.

Public health relevance

GLOBOCAN estimates the worldwide total leukaemia incidence in 2012 to be 351 965 cases, with an age-standardized rate (ASR) of 4.7 per 100 000. The incidence of leukaemia in more-developed regions in 2012 was estimated as 141 274 (ASR of 7.2 per 100 000) compared with 210 691 (ASR of 3.8 per 100 000) in less-developed regions *(16)*. GLOBOCAN does not provide specific information about CLL.

A USA study published in 2004 estimated the worldwide incidence of CLL to be between <1 and 5.5 per 100 000 people *(17)*; the highest incidence rates that year were found to be in Australia, Ireland, Italy and USA. The study suggested that CLL is more common in adult males than in females and in Caucasians than in people of black race. The median age of diagnosis is between 64 and 70 years. In the USA in 2004, five-year survival rate was 83% for those under 65 years of age and 68% for those aged 65 years and above. In Germany about 3000 men and 2000 women are newly diagnosed with CLL each year, with the median age at diagnosis being between 70 and 75 years *(18)*. Family history of CLL is a noted risk factor for development of the disease *(19)*.

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 assessment is performed only to assess marrow reserves and for genetic analysis before treatment and to assess response after completion of treatment. After initial therapy,

minimal residual disease – detectable by flow cytometry in marrow or blood – in patients in remission 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 adverse effects such as anaemia, neutropenia and thrombocytopenia. Autoimmune haemolytic anaemia occurs in approximately 15% of patients with CLL; the direct antiglobulin test, together with biochemical analysis for bilirubin and lactate dehydrogenase, is important to diagnose and monitor this complication. A bone marrow examination is important for evaluation before treatment and for assessing response *(20)*. Flow cytometric evaluation is also important for monitoring response.

Where available, fluorescence in-situ hybridization or karyotypic analysis is essential to detect the common adverse genetic abnormalities (11q- and 17p-), but adds 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 *(20)*.

Administration and care of patients

Administration requires intravenous infusion capacity for rituximab and regular patient access to clinical care. Fludarabine and cyclophosphamide may be given intravenously or orally. In developed countries, rituximab administration is usually performed in outpatient facilities; in other settings, however, patients may be treated in inpatient facilities. Rituximab can cause severe allergic reactions and must be given slowly, with premedication including steroids and antihistamines; close monitoring is essential and additional supportive medicines must be 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 well-being can be impacted by treatment side-effects and should also be monitored and addressed.

Patients with CLL should be followed indefinitely in view of the risk of disease relapse and further progression, and the 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, the long-term outlook for patients who progress within 2–3 years after front-line FCR was grave until recently when B-cell receptor pathway inhibitors became available.

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 progression-free survival, permitting a normal quality of life for a

substantial period of time. This permits patients to continue to work and remain productive while their families reach maturity, resulting in a major social and psychological benefit for patients, their families and society. By contrast, elderly or infirm patients may have different treatment goals and the shorter period and less complete degree of disease control achieved with chlorambucil may be appropriate. Chlorambucil is already included in the List of Essential Medicines, and the application recommends it remain on the list for palliative care in CLL patients.

Overview of regimens

The regimens below include basic information on administration and dosing for treatment of CLL. The FCR regimen may be administered intravenously or orally, but it is important to note that the dose and duration of the FC component are different in the intravenous and oral regimens. The protocols exclude ancillary medications for the management of side-effects (e.g. prophylactic growth factor support to minimize neutropenia, and prophylactic antibiotics and antivirals to minimize infection risk).

Standard regimens

- **FCR regimen (planned 6 cycles)**

Note difference in doses and duration with IV vs. oral regimen. These IV and oral regimens are considered approximately dose-equivalent.

Using intravenous FC over 3 days

- fludarabine 25 mg/m^2 IV on days 1–3
- cyclophosphamide 250 mg/m^2 IV on days 1–3
- rituximab 375 mg/m^2 IV on day 1 of cycle 1, then 500 mg/m^2 on day 1 of cycles 2–6

Using oral FC over 5 days

- fludarabine 24 mg/m^2 orally on days 1–5
- cyclophosphamide 150 mg/m^2 orally on days 1–5
- rituximab 375 mg/m^2 IV on day of cycle 1 then 500 mg/m^2 on day 1 of cycles 2–6

- **Standard bendamustine–rituximab regimen (every 4 weeks; 4 cycles)**

- bendamustine 90 mg/m^2 IV on days 1 and 2
- rituximab 375 mg/m^2 IV on day 1

Note: It is recommended that rituximab be used as outlined above but, if it is unavailable or unaffordable, it can be omitted from these regimens. The results are inferior to rituximab-containing regimens, but benefit is still substantial.

The FCR regimen universally causes neutropenia. This in turn is commonly treated with growth factor support (granulocyte-colony stimulating factor, G-CSF), which may significantly increase therapy-related costs. The addition of G-CSF to the EML was considered in a separate application.

- **Alternative regimen for advanced symptomatic disease: R-CVP (every 3 weeks; 6 cycles)**
  - rituximab 375 mg/m^2 IV on day 1
  - cyclophosphamide 750 mg/m^2 IV on day 1
  - vincristine 1.4 mg/m^2 IV (cap dose at 2 mg) on day 1
  - prednisone 100 mg orally on days 1–5

  Note: It is recommended that rituximab be used as outlined above, but if it is unavailable or unaffordable, this regimen can be used without rituximab. The results are inferior to rituximab-containing regimens, but benefit is still substantial.

Assessment of CLL response to therapy requires a bone marrow biopsy and imaging to document response as detailed in the International Workshop on CLL guidelines *(20)*. Clearance of CLL cells from the peripheral blood is not an adequate therapy end-point and does not represent complete response.

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 *(21)*.

Review of benefits and harms

Benefits

A large randomized controlled trial in the United Kingdom, the LRF CLL4 trial, documented the superiority of fludarabine plus cyclophosphamide (FC) to either fludarabine or chlorambucil alone in terms of median PFS – 43 months (95% CI: 35–51), 23 months (95% CI: 18–27,) and 20 months (95% CI: 18–22), respectively *(22)*. However, there were no significant differences in survival between treatment groups: at 5 years, survival was 59% (95% CI: 53–66) with chlorambucil, 52% (95% CI: 42–61) with fludarabine, and 54% (95% CI: 44–64) with FC. Subsequently, the large randomized CLL8 trial showed that the addition of rituximab to FC (FCR chemoimmunotherapy) produced superior results: PFS was longer in the chemoimmunotherapy group than in the chemotherapy group (median 51.8 months (95% CI: 46.2–57.6) versus 32.8 months (95% CI: 29.6–36.0)) *(23)*. The CLL8 study planned six cycles of FCR therapy; most patients tolerated this treatment. The CLL8 study also documented that twice as many patients achieved a complete response (CR), and minimal residual disease (MRD) negativity, with six cycles than with three cycles of treatment *(24)*. Generally, therefore, six cycles of therapy are 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 *(20)*.

A subsequent Cochrane systematic review cumulated results from three randomized controlled trials (n = 1421) assessing the efficacy of monoclonal anti-CD20 antibodies (i.e. rituximab) plus chemotherapy compared with chemotherapy alone *(25).* The meta-analyses showed a statistically significant advantage for patients receiving rituximab in terms of overall survival (hazard ratio (HR) 0.78; 95% CI: 0.62–0.98) and progression-free survival (HR 0.64; 95% CI: 0.55–0.74). The number needed to treat for an additional beneficial effect was 12. Hence combination immunochemotherapy with FCR is now the standard of care for younger, fit patients; the time to second therapy with FCR is reaching 5–7 years compared with approximately 2 years with chlorambucil, and better quality of life reflects the much longer period of excellent disease control with FCR.

The LRF CLL4 trial began by using the FC combination intravenously over three days. During the course of the trial, an orally administered schedule was introduced, which administered the same drugs over five days rather than three *(22).* An Australian study that focused on fit patients aged 65 years and over also adopted this five-day oral regimen as the method of administration *(26)*, while the CLL-8 trial used the three-day intravenous schedule.

In a multicentre phase II trial by the German Chronic Lymphocytic Leukemia Study Group, safety and efficacy of bendamustine and rituximab were investigated in previously untreated patients with CLL. It was demonstrated that 90.5% of patients were alive at 27 months, and the median event-free survival was 33.9 months *(13)*. These findings led to testing the non-inferiority in terms of efficacy and tolerability of BR compared to FCR as first-line therapy in physically fit patients with advanced CLL without del(17p) in a randomized controlled trial: the CLL10 trial *(14).* Results of a planned interim analysis showed FCR to be associated with a better complete response rate (CRR), PFS and event-free survival (EFS) than BR. CRR for FCR was 47.4% compared to 38.1% for BR (P = 0.031). Overall survival rates were the same in each treatment arm, however the duration of follow-up was too short to exclude potentially relevant differences between arms. With regard to adverse events, myelosuppression was more frequent in the FCR arm compared to the BR arm, with higher rates of severe haematotoxicity (90.0% vs 66.9% P < 0.001), severe neutropenia (81.7% vs 56.8%; P < 0.001), and severe infections (39.0% vs 25.4%; P = 0.001), especially in the elderly.

For patients who have comorbidities or are unable to tolerate one of the regimens outlined above, Cbl with the novel CD20 antibody obinutuzumab has been documented as superior to Cbl with rituximab which was in turn superior to Cbl alone in the large CLL11 study *(27)*.

Harms and toxicity considerations

Common

Rituximab can cause allergic reactions and must be given slowly, with premedication including steroids and antihistamines; close monitoring is essential and supportive

medicines must be 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% *(11, 12, 23)*. Myelosuppression with this regimen may persist for more than 3 months and commonly requires growth factor support to shorten the duration of neutropenia and reduce the risk of infections *(23, 28)*. Thrombocytopenia and anaemia also occur, and blood transfusion support is frequently required.

Data regarding grade 3–4 adverse events are heterogeneous across trials. Reported grade 3 or 4 infection-related adverse events may be higher in patients treated with bendamustine compared with fludarabine *(25)*; other grade 3 and grade 4 adverse events with bendamustine and fludarabine may be similar. The effect of bendamustine on quality of life is similar to that of chlorambucil.

Recommendations

On the basis of the evidence presented, the Expert Committee made the following recommendations in relation to treatments for chronic lymphocytic leukaemia:

- addition of fludarabine (oral and IV formulations) and rituximab to the complementary list of the EML;
- addition of bendamustine to the complementary list of the EML;
- endorsement of cyclophosphamide, vincristine and prednisone, already included on the complementary list, specifically for the treatment of CLL;
- endorsement of chlorambucil for use in palliative chemotherapy for CLL.

The Committee recommended that, in settings where rituximab is not available or affordable, the treatment regimens detailed in the application should be used without rituximab. The clinical benefits associated with their use, while not as great as when combined with rituximab, are nonetheless substantial and clinically relevant.

The Expert Committee acknowledged that the FCR regimen has been shown to be superior to FC for all clinical outcomes, including overall survival, in young and fit patients, and is the standard first-line treatment regimen for CLL. However, the Committee also noted that this disease occurs at a median age over 70 years, and comorbidities in this patient population may make FCR tolerability a major issue for a proportion of elderly patients. Based on its efficacy and safety profile the Committee considered that first-line treatment with bendamustine, either alone or in combination with rituximab, is a reasonable alternative to FCR in patients for whom FCR is not appropriate or not tolerated (e.g. older patients), or in patients wishing to improve quality of life or decrease toxicity.

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