

Chronic lymphocytic leukaemia: An updated approach to diagnosis and management in general practice

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Background

Chronic lymphocytic leukaemia (CLL) is the most common lymphoproliferative disease in Australia. Improvements in the understanding of this disease have led to drastic changes in regards to diagnosis, management and prognosis.

Objectives

The aim of this article is to give an updated approach to the diagnosis, investigation, monitoring and new treatments of CLL.

Discussion

With the advent of new medications and improved investigations to predict outcomes, CLL has now become a chronic disease that requires long-term monitoring by haematologists and general practitioners (GPs).

The outlook for patients with chronic lymphocytic leukaemia (CLL) has changed drastically over the past decade. These changes come primarily from the advent of new monoclonal antibodies and novel therapies applied to an ageing population with increasing comorbidities.

CLL is a lymphoproliferative disease that produces immunologically immature cells. These cells accumulate in peripheral blood and have a solid component that can be found primarily in lymph nodes and bone marrow. Recent population studies have found that approximately 1174 patients were diagnosed with CLL in 2012, with 342 deaths as a result of the disease. The incidence of the disease increases with age, as does mortality rate.¹

The diagnosis of CLL is often made incidentally on a routine full blood count, showing lymphocytosis (total lymphocyte count $>5.0 \times 10^9$). The immunophenotype displayed on flow cytometry shows a monoclonal population of mature B lymphocytes expressing a unique phenotype of CD19+, CD20+, CD5+ and CD23+. When this cell pattern is seen exclusively on lymph node biopsy with peripheral blood component $<5 \times 10^9$, the diagnosis is small lymphocytic lymphoma (SLL). The World Health Organization (WHO) considers SLL and CLL to be biologically the same disease.²

The flow cytometry pattern for CLL

can also be seen with monoclonal B-cell lymphocytosis (MBL), a premalignant disease. The defining feature of MBL is an absolute lymphocyte count of $<5.0 \times 10^9$. The risk of progression from MBL to frank CLL occurs in 1–2% of patients per year (Table 1).³

Signs and symptoms

Signs and symptoms of CLL include:

- cytopenias
 - anaemia
 - leukopenia/neutropenia, with increased risk of infections
- thrombocytopenia, with increased risk of bleeding
- lymphadenopathy and splenomegaly
- constitutional symptoms of malignancy (eg weight loss $>10\%$ in six months, fevers, night sweats).

Anaemia can either be a result of disease progression, with replacement of normal marrow with CLL cells, or autoimmune haemolytic anaemia.⁴ Similarly, thrombocytopenia can be a result of bone marrow failure or from an autoimmune process.

Diagnostic work-up

History, physical examination and simple blood tests are key to the detection of complications of cytopenias and staging of CLL. Blood tests required include:

- full blood count
- urea, electrolytes and creatinine

- liver function tests
- serum immunoglobulin levels and Coombs test
- diagnostic flow cytometry on peripheral blood
- viral serology (ie hepatitis B, hepatitis C, human immunodeficiency virus, Epstein-Barr virus and cytomegalovirus).

Computed tomography (CT) scans of the chest, abdomen and pelvis are used to identify the degree of lymphadenopathy, and are often ordered in the initial diagnostic stages to exclude other differential diagnoses. Bone marrow biopsy is not required for the diagnosis of CLL, but is recommended for the evaluation of unexplained cytopenias.

Additional tests to aid in prognosis and selected therapies

Fluorescent in situ hybridisation (FISH) is used to detect cytogenetic changes (Table 2). Molecular studies are used to detect the mutational status of immunoglobulin heavy chain variable (*IgHV*) genes. Unmutated *IgHV* are more prone to genetic errors and, subsequently, have poorer overall survival.⁵

Additional investigations include ZAP-70 expression and CD38 expression on flow cytometry, which is a surrogate measure of *IgHV* mutational status. ZAP-70 and CD38 are primarily used in research settings and currently do not influence therapeutic outcomes.

Management

Management of CLL is dictated by the stage, presence of symptoms, and individual patient preference. Current treatment for CLL ranges from

monotherapy to combination therapy with chemotherapy and immunomodulatory agents. Currently, the standard therapy for patients who are fit is a combination of fludarabine, cyclophosphamide and rituximab (FCR).

There is no specific age cut-off for therapy. Rather, fitness for therapy is derived from physical fitness and comorbidities. New agents that have become available in the past several years are listed in Table 3.

Ibrutinib

Ibrutinib is an oral, selective inhibitor of Bruton's tyrosine kinase, an important regulator in the B-cell receptor signalling pathway, and subsequently inhibits B-cell proliferation. Current indications for the use of ibrutinib in Australia include first-line therapy for CLL with 17p deletion, and second-line therapy for CLL or SLL (after at least one previous therapy).

Approval for the use of ibrutinib was based on a phase III clinical trial comparison with ofatumumab. Patients received ibrutinib at a dose of 480 mg until disease progression or intolerable adverse events resulted; a majority of patients in the study had unfavourable cytogenetics (eg 17p deletion or 11q deletion).⁶ Progression-free survival and overall survival were longer for patients treated with ibrutinib than those treated with ofatumumab. Patients with poor-risk disease also had better outcomes.⁶

Ibrutinib-associated lymphocytosis occurred in 73% of patients, peaking at a median of four weeks, then declining at a rate dictated by the disease risk factors. Patients with good prognosis cytogenetics

had slower declines, whereas those with higher risk disease had faster declines. All cases of lymphocytosis were asymptomatic and resolved by week 19.⁷ Notable adverse events included increased rates of diarrhoea (4% versus 2%), atrial fibrillation (3% versus 0%), infection rates (70% versus 54%) and risk of bleeding.⁶ Ibrutinib-induced bleeding can either be due to its effect on platelet function or when anticoagulation is used to treat atrial fibrillation.

Idelalisib

Idelalisib is a potent, oral, selective, small-molecule inhibitor of phosphatidylinositol-3-kinase δ (PI3K δ), a key component in the B-cell receptor signalling pathway. Phase III data included older patients with heavily pretreated disease who were ineligible for systemic chemotherapy because of cytopenias, and received idelalisib with rituximab or rituximab alone.⁸ Progression-free survival was higher in the idelalisib group, compared with the control group. Overall survival was also superior, even in those with poor-risk cytogenetics.

Specific adverse effects included cytopenias (eg anaemia, neutropenia, thrombocytopenia) and hepatic aminotransferase elevation. Drug discontinuation due to adverse events was 8% in the trial group and 10% in the placebo group.⁸ Idelalisib also caused drug-associated lymphocytosis, with an increase in total lymphocytes, which occurred within the first weeks of drug therapy. This peaked at week two and resolved by week 12.⁸ This elevation is not considered a sign of disease progression.

Ofatumumab

Ofatumumab is a fully human monoclonal antibody, which was found to be effective in the treatment of CLL. It is given by infusion in hospital chemotherapy day units. The results were from an international, randomised phase III trial comparing ofatumumab plus chlorambucil therapy with chlorambucil monotherapy. Ofatumumab led to improved

Table 1. Rai staging (clinical predictors of prognosis)

Rai stage	Modified Rai risk	Clinical characteristics
0	Low	Lymphocytosis in peripheral blood and bone marrow only
1	Intermediate	Lymphocytosis and enlarged lymph nodes
2	Intermediate	Lymphocytosis and enlarged liver or spleen
3	High	Lymphocytosis and anaemia (haemoglobin <110 g/L)
4	High	Lymphocytosis and thrombocytopenia (platelets <100 x 10 ⁹)

Table 2. Cytogenetics (FISH) and median overall survival (OS)¹⁷

Cytogenetic change	Characteristics	Median OS
Del17p	<ul style="list-style-type: none"> Associated with rapidly progressive disease Potentially warrants different upfront therapy to standard risk disease (eg ibrutinib) 	33 months
Del13q	<ul style="list-style-type: none"> Good prognosis if low allelic burden Long response to fludarabine therapy 	133 months
Del11q	<ul style="list-style-type: none"> Seen in younger age, male patients Frequently associated with bulky disease and poor prognosis 	79 months
12q trisomy	<ul style="list-style-type: none"> Intermediate prognosis 	114 months

progression-free survival in all patients, including those with poor prognostic factors. It did not have an effect on overall survival.⁹

Obinutuzumab

Obinutuzumab is a humanised type 2 antibody targeting CD20 antigen on B cells. It is given by infusion in a chemotherapy day unit. It is primarily given to older patients who cannot tolerate chemotherapy (eg fludarabine), in whom it is given together with chlorambucil. A phase III trial of 781 previously untreated patients compared obinutuzumab plus chlorambucil, rituximab plus chlorambucil, and chlorambucil alone.¹⁰ Obinutuzumab plus chlorambucil had increased response rates and progression-free survival, compared with chlorambucil monotherapy. There was no difference in overall survival when obinutuzumab plus chlorambucil was compared with rituximab plus chlorambucil. Obinutuzumab had higher rates of neutropenia, but had similar rates of infections. Patients had higher rates of infusion reactions that were treated well with steroids, paracetamol and antihistamines.¹⁰

The summary of the trial revealed that obinutuzumab with chlorambucil was an appropriate treatment for older patients with CLL who are unfit, and had improved outcomes and equivalent overall survival, but higher toxicity, compared with chlorambucil or rituximab plus chlorambucil.

Follow-up

CLL remains an incurable disease, and lifelong follow up of patients is necessary. Evaluation is dictated by patient and disease factors. For those with mild or relatively stable disease, follow-up every three to 12 months is adequate. Warning signs for general practitioners when following up patients with CLL include:

- lymphocytes doubling within three to six months
- lymphadenopathy causing symptoms
- progressive cytopenias as a result of bone marrow failure or autoimmune phenomena
- constitutional symptoms (eg weight loss >10% within six months, fevers, night sweats, significant fatigue).

These are often signs that the patient requires urgent or semi-urgent treatment, and they should be referred to a haematologist as soon as possible.

Transformation into either Hodgkin's

lymphoma or diffuse large B-cell lymphoma (DLBCL) occurs at a rate of 2–15%.¹¹ Clinical signs include increasing cytopenias, increased constitutional symptoms or new lymphadenopathy. Diagnosis is confirmed on lymph node histology, and treatment is based around de novo treatment for the respective condition.

Second malignancies are common in patients with CLL. The most frequently encountered second malignancies are non-melanoma skin cancers. Patients with CLL have increased rates of local recurrence, regional metastasis and death from skin cancers. Education regarding sun protection and frequent skin cancer checks, every six to 12 months, are fundamental.¹² Patients are at an increased risk of solid organ cancers, and age-appropriate cancer screening (eg prostate, breast, bowel cancer) should be adhered to.¹³

Infections are also increased in patients with CLL, owing to disease factors and treatment complications. Hypogammaglobulinaemia is frequently seen because of CLL and therapy (specifically rituximab).¹⁴ If the patient has low globulin levels, specifically immunoglobulin G, and frequent bacterial infections, intravenous immunoglobulin monthly, or subcutaneous immunoglobulin weekly can help reduce infections.¹⁵ Yearly influenza vaccination and pneumococcal vaccination are also recommended. Specific vaccination schedules are available in the *Australian immunisation handbook*.¹⁶

Table 3. CLL treatment and mechanism of action

Older treatment	Mechanism of action
Chlorambucil monotherapy	Alkylating agent – disrupts DNA
Fludarabine-based therapy	Alkylating agent – disrupts DNA
Rituximab	Anti-CD20 monoclonal antibody
Newer treatment	Mechanism of action
Ibrutinib	Bruton's tyrosine kinase inhibitor
Ofatumumab plus chlorambucil	Anti-CD20 monoclonal antibody
Obinutuzumab plus chlorambucil	Anti-CD20 monoclonal antibody
Idelalisib	Phosphatidylinositol-3-kinase inhibitor

Key points

- CLL is a rapidly changing disease, owing to more sensitive investigations and new medications.
- CLL is diagnosed most commonly on routine blood tests, before patients experience symptoms.
- Symptoms are related to low blood counts, infections, mass effect from lymph nodes and autoimmune complications.
- Investigations include full blood count, viral serology, flow cytometry and molecular studies (ordered by haematologists).
- New medications include an array of chemotherapy, immunotherapy and targeted therapy, all with unique adverse effects.
- Follow up is generally lifelong, and patients are at increased risk of secondary and skin cancers, and infections.

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