



Treatment of chronic lymphocytic leukaemia

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Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia diagnosed in the western world, with an annual incidence of 3-4/100,000 population. This equates to 60-80 new cases per year in WA. As a significant number of patients with CLL may live for many years, the prevalence is higher and therefore quite frequently encountered in medical practice. There have been significant advances in the treatment of CLL in recent years and ongoing research will likely translate into further improvement in outcomes for patients.

Pathogenesis

CLL is characterised by the progressive accumulation of B-lymphocytes in the peripheral blood. Looking down the microscope, they appear as small, mature lymphocytes and a typical finding is the presence of smear cells. Diagnosis can be confirmed by flow cytometry which shows the co-expression of CD5 with the normal pan-B-cell antigens (CD19 and 20). Despite their relatively normal appearance, these B-cells are functionally abnormal. They are often very resistant to apoptosis, which accounts in large part for their progressive accumulation in the blood. Apoptosis resistance is mediated primarily through over expression of the bcl-2 oncogene. This defective function is also responsible for some of the complications of CLL, including hypogammaglobulinemia and autoimmune haemolytic anaemia and thrombocytopenia. The clinical course can be quite variable and the molecular basis of this diversity is being investigated. Cytogenetic analysis of the leukaemic cells, in particular, can help predict the likelihood of progressive versus indolent disease (with deletions of chromosomes 17p, harbouring the p53 locus, and 11q being associated with more aggressive disease).

Presentation

The majority of patients are diagnosed after finding lymphocytosis on a full blood count, often performed for unrelated reasons, while others can present with lymphadenopathy, fatigue and systemic symptoms related to the disease.

CLL follows a variable clinical course, with some patients having indolent disease not requiring treatment for many years, if ever, while others progress much more rapidly.

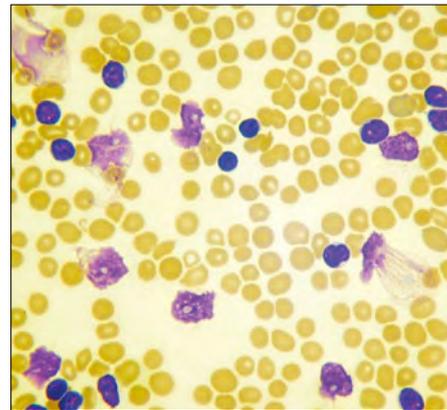
In the individual patient, the decision to institute treatment remains based predominantly on clinical factors.

Clinical approach to treatment

When faced with a patient with newly diagnosed CLL, two questions need to be addressed:

1. Does the patient require treatment?
2. If the answer is yes, what treatment is best for this patient?

CLL is still considered an incurable disease and while patients usually respond well to



■ Blood film from a patient with CLL showing small, mature lymphocytes and smear cells.

Table 1: Progress in first line treatment for CLL

Era	Therapy	Complete remission	Avg time of remission
1970's	Alkylators	5%	1-2 years
1980's	Fludarabine	20%	2-3 years
1990's	FC	35%	3-4 years
2000's	FCR*	>50%	4-7 years

*Rituximab is not currently PBS-reimbursed for primary treatment of CLL.

chemotherapy, most will relapse at some point in the future. Therefore treatment is reserved for patients with complications or symptoms related to the CLL.

Patients with early stage disease, characterised by a lymphocytosis without lymphadenopathy/splenomegaly or evidence of bone marrow failure, do not require treatment. The good news is that this is the largest group of CLL patients and many will never require treatment.

Patients with more advanced CLL may be suitable for a period of observation to judge the "tempo" of the disease. There is no defined lymphocyte count that automatically triggers treatment and even patients with counts in excess of 100,000 may not require immediate treatment.

There are well established guidelines for the initiation of treatment in CLL. These include:

1. Progressive bone marrow failure (anaemia, neutropenia or thrombocytopenia)
2. Massive or progressive lymphadenopathy
3. Massive or progressive splenomegaly
4. Progressive lymphocytosis
5. Systemic symptoms (e.g. fever, sweats) due to the CLL

Choosing treatment

Once a decision is taken to institute treatment, the clinician needs to decide the best therapy for the individual patient.

Traditionally, alkylating chemotherapy drugs such as chlorambucil were used to control the lymphocyte count and improve symptoms. However, chemotherapy drugs with a far greater activity against CLL are now available and there has been a shift from an essentially palliative approach to using drug combinations that greatly prolong the time until further therapy is needed.

Fludarabine is a very effective drug in CLL and, when combined with cyclophosphamide

("FC"), significantly improves remission rates and disease free intervals. The addition of rituximab, a monoclonal antibody, to form the "FCR" combination further improves results and is currently the most active combination available for CLL. Using sensitive PCR and flow cytometric assays, FCR completely eradicates the CLL clone in a significant proportion of patients.

Table 1 shows the improvement in results for treatment of CLL over the last four decades.

The more active drug combinations prolong the period of remission and appear to be changing the natural history of CLL with evidence to support improvement in overall survival. They do, however, have more side-effects and need to be used judiciously in the more elderly patients.

Despite these significant improvements, some patients will become refractory to chemotherapy and die of CLL. It is important to recognise when chemotherapy is no longer working and introduce appropriate palliative care measures rather than persist with potentially toxic treatment.

Associated problems

CLL is associated with a number of complications which may also require treatment.

Autoimmune haemolytic anaemia and thrombocytopenia are well recognised and treated with prednisolone and/or rituximab.

Infection is common and requires prompt assessment. Some patients with recurrent infection and hypogammaglobulinaemia need intravenous immunoglobulin replacement therapy.

Patients with CLL have more than twice the risk of developing a second cancer. Skin cancer rates are particularly high and vigilant sun protection measures and early assessment of solar damage are important. ■