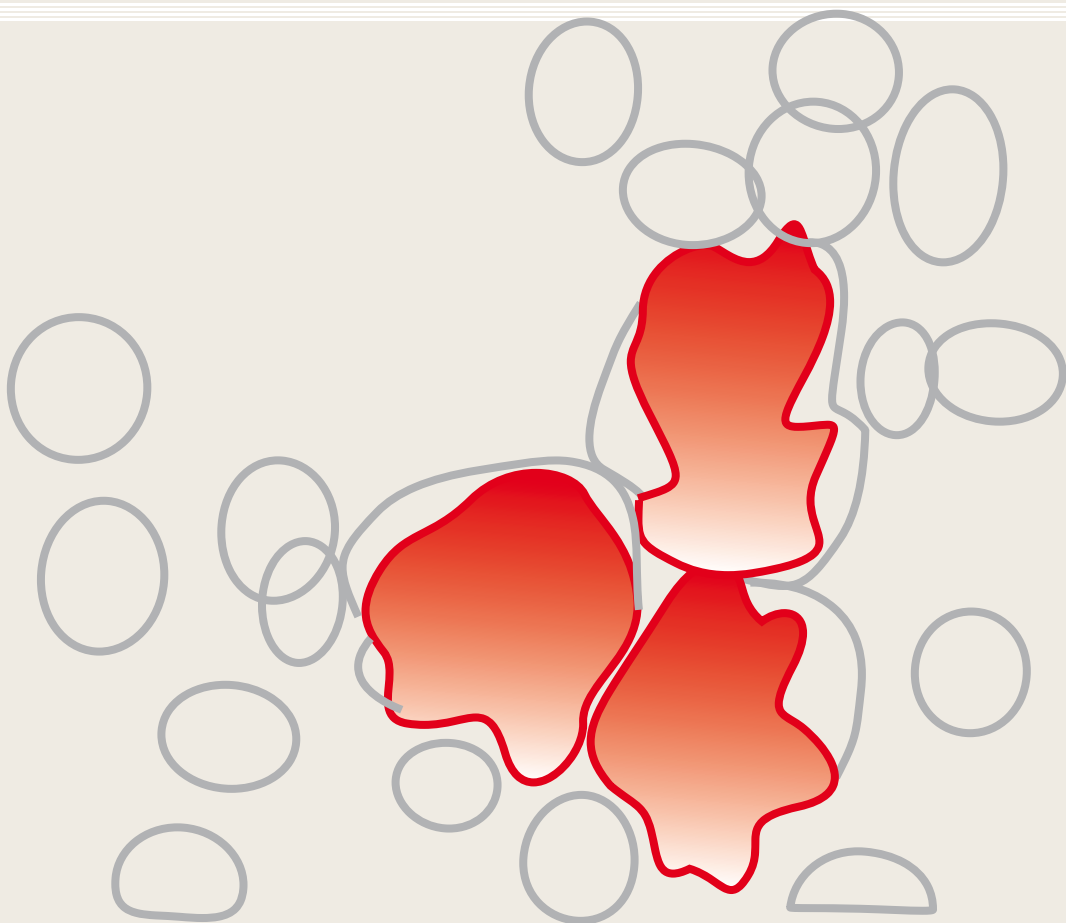


Chronic Lymphocytic Leukaemia (CLL)



The diagnosis of a blood cancer can be a devastating event for patients, families and friends. It is therefore vital for everyone to have access to reputable and understandable information to help cope with the illness. Whenever possible our booklets are written in line with national guidelines for the treatment of patients with a blood cancer. The information in our booklets is more detailed than in many others but is written in a clear style with all scientific terms explained for the general reader.

We recognise that the amount and level of information needed is a personal decision and can change over time. Particularly at the time of diagnosis, patients may prefer less detailed information. A number of alternative sources of information are available which complement our publications.

The booklets in this series are intended to provide general information about the diseases they describe. In many cases the treatment of individual patients will differ from that described in the booklets.

At all times patients should rely on the advice of their specialist who is the only person with full information about their diagnosis and medical history.

For further advice contact the clinical information team on 020 7269 9060.

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What is chronic lymphocytic leukaemia?

Chronic lymphocytic leukaemia (CLL) is a form of leukaemia in which there is an excess number of mature, but poorly functioning, lymphocytes in the circulating blood. In CLL, the major reason for the build-up of tumour cells is the failure of lymphocytes to die at the end of their normal life span. The rate of production of lymphocytes is not significantly increased and may even be lower than normal.

Lymphocytes are white blood cells that are vital parts of the body's immune system. Lymphocytes can be classified into sub-groups according to their function — the main groups are B cells and T cells. This is called immunophenotyping. All cases of CLL and most lymphomas (tumours of glands) affect the B cells. T cell leukaemias are extremely rare.

Many patients with CLL also have autoimmune disease, which occurs when the body produces antibodies against its own tissues. These antibodies destroy the patient's own red blood cells causing anaemia and/or destroy the platelets. The spectrum of conditions seen includes autoimmune haemolytic anaemia (10% of patients), autoimmune platelet destruction and a combination of both.

About 15% of patients will undergo a subtle transformation of CLL to a more rapidly progressing condition. This is called chronic lymphocytic leukaemia/prolymphocytic leukaemia (CLL/PLL), in which there are increased numbers of prolymphocytes; the other form of transformation or Richter's syndrome (rapidly progressing large cell lymphoma in a patient with CLL) is more dramatic and occurs in 5-10% of cases.¹ At present, there is no test available to predict which patients are likely to undergo transformation of their disease but there are a considerable number of clinical features and laboratory tests which help to predict overall outcome.

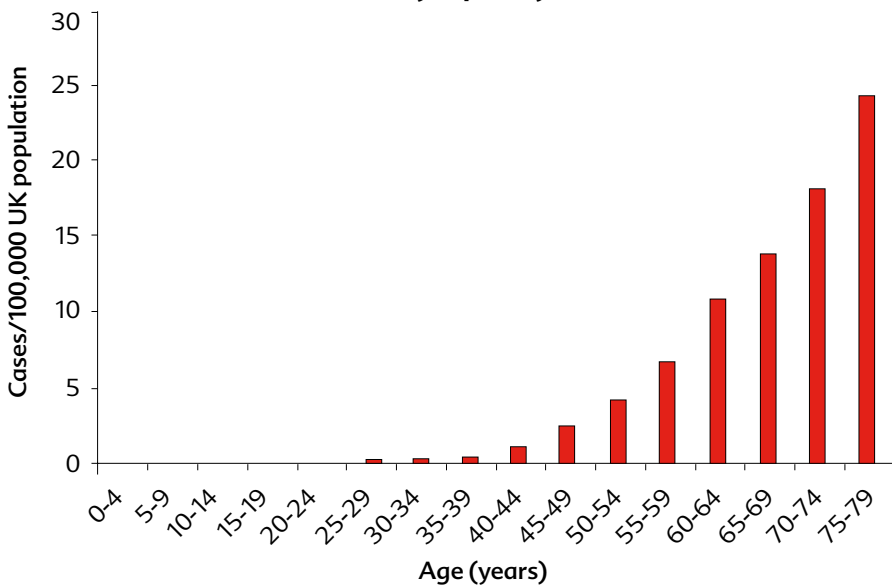
¹ There is a separate publication on transformation of CLL available from Leukaemia Research.

Who gets chronic lymphocytic leukaemia?

Chronic lymphocytic leukaemia is overwhelmingly a disease of later life; it makes up 40% of all leukaemia in patients over 65 years old. The overall incidence is about 3/100,000 per year with an average age of onset of 65 to 70 years.

Only about 20-30% of patients are younger than 55 years of age at the time of diagnosis. There is an overall male excess which is less marked with increasing age – the ratio is about 2 to 1. The incidence in black and white populations is approximately equal but the disease is rare in Asians. The scarcity in Asians is seen regardless of where they are resident and of their lifestyle, which suggests that this may reflect underlying differences in susceptibility.

Incidence of chronic lymphocytic leukaemia in the UK



What are the types of chronic lymphocytic leukaemia?

Chronic lymphocytic leukaemia shows an extremely wide variation in its clinical features. There is no formal classification system like those which exist for the acute leukaemias and lymphomas. Many studies have been carried out to develop ways of predicting which patients are likely to have a long survival and which may have more rapidly progressing disease. These include clinical staging based on signs, symptoms and the results of laboratory tests as discussed below.

CLL related diseases

There are several conditions sometimes referred to as variant CLL. These are not just variants but are recognised to be separate disease entities related to CLL. A scoring system has been devised which considers various features of the abnormal cells, mainly based on immunological typing (this detects the presence of certain molecules or antigens on the surface of the lymphocytes and CLL cells), and is helpful to distinguish CLL reliably from similar conditions including the following:

∴ B cell prolymphocytic leukaemia

This is a distinct disease entity in which almost all the leukaemia cells are larger than those seen in typical CLL. The cells have a distinctive appearance and are described as prolymphocytes. This leukaemia is different from the prolymphocytic transformation of CLL in which there is a mixture of CLL cells and prolymphocytes.

The lymphocyte count is often very high at diagnosis – $100 \times 10^9/l$ or greater. Polymphocytic leukaemia responds poorly to single drug treatment such as that used for typical CLL. Treatment with drug combinations of the type used for non-Hodgkin's lymphoma may be more effective. The overall prognosis is less favourable than for CLL with a median survival of about three years.

∴ Leukaemic phase of non-Hodgkin's lymphoma

Patients with non-Hodgkin's lymphoma usually have few or no lymphoma cells in their blood at the time of diagnosis. Rarely, they may present with a leukaemia resembling CLL. In later stages of the disease, they may progress into a leukaemic phase, in which lymphoma cells are easily detected in the blood. Most types of non-Hodgkin's lymphoma are easily distinguished from CLL because the malignant cells look very different and the results of immunological typing are quite different.

There are many types of lymphomas; in one type, called small lymphocytic lymphoma (SLL), the lymphoma cells closely resemble the leukaemia cells seen in CLL. The distinction between SLL and CLL is based on the clinical behaviour of the disease; if the most prominent feature is enlarged lymph nodes with little disease in the marrow or blood, then the diagnosis is SLL. If there is a marked involvement of the bone marrow and blood at the time of diagnosis it is classified as CLL.

∴ Hairy cell leukaemia²

Another related condition is hairy cell leukaemia which affects B cells but has very distinct morphology (the appearance of the cells under the microscope) and clinical features.

∴ T cell chronic lymphoproliferative diseases

There is no such thing as T CLL. The T cell chronic lymphoproliferative diseases include large granular lymphocytic leukaemia, T cell prolymphocytic leukaemia and the leukaemic phases of various T cell lymphomas.

What causes chronic lymphocytic leukaemia?

There are no clearly defined risk factors for chronic lymphocytic leukemia. No environmental exposures (radiation, chemicals, or infections) have been shown to increase the risk of developing CLL. There is some evidence of an association between exposure to agricultural chemicals and certain viruses with an increased risk of CLL, but this evidence is inconclusive. Intriguingly, there have been more cases of CLL reported in the spouses of patients than chance would predict. This suggests the possibility of shared environmental factors affecting the risk.

The only factors definitely associated with an increased risk of CLL are older age and male sex. CLL is unknown in childhood, rare in young adults and becomes progressively more common from the age of about 35 years. A higher number of males are diagnosed with CLL compared to females.

There is strong evidence of genetic differences in susceptibility to CLL. In Asian populations the incidence of CLL is very low, whether they have an Asian or a western lifestyle. Further evidence for a genetic component is the increased incidence of CLL and related conditions in close relatives of CLL patients. It has been estimated that as many as 10% of all cases may be familial. When this occurs it is common for CLL to be diagnosed at a younger age in each succeeding generation.



What are the signs and symptoms of chronic lymphocytic leukaemia?

About 70-80% of all new cases of CLL are chance findings on a routine blood test, and between 40% and 60% of patients with CLL are free of symptoms at the time they are diagnosed. Almost all of these cases are discovered as a result of enlarged lymph nodes being noted by a doctor at a routine check-up or, more frequently, by abnormal results from routine blood tests. The number of asymptomatic cases discovered depends on the proportion of a given population having regular physical examinations or blood counts. It is common for there to be no symptoms at the time of diagnosis even when the white blood cell count is very high ($>100 \times 10^9/l$).

In those patients who have symptoms at the time they are diagnosed, these are most commonly weakness, fatigue, night sweats or proneness to repeated infections. On being examined, these patients have enlarged but not tender lymph nodes and enlarged liver, or spleen, or both. About 15% of patients will either be anaemic (low haemoglobin levels) or have a low platelet count. This shows that the disease has affected the normal production of blood cells in the bone marrow or that there has been auto-immune damage to the red cells or platelets.



How is chronic lymphocytic leukaemia diagnosed?

Unlike acute leukaemia, chronic lymphocytic leukaemia is not considered a medical emergency. Most patients have a relatively slowly progressing (indolent) form of the disease. If it is diagnosed early, it is not usual to start treatment immediately. For this reason, it is perfectly normal for a patient who is thought to have CLL to be given a non-emergency appointment to see a hospital specialist.

Diagnosis of CLL is usually based on blood count and immunophenotyping (tests that look for specific proteins on the surface of the cancer cells). For a diagnosis of CLL to be made the lymphocyte count must be at least $5 \times 10^9/l$ and the other features of CLL must be present. In all other forms of leukaemia a bone marrow sample is routinely obtained at the time of first diagnosis. Patients with early-stage CLL who are free of symptoms are not candidates for active treatment. In this group of patients, clinicians may elect not to take bone marrow samples. Bone marrow samples are less likely to be taken in older patients with slowly progressing disease. However, if there is any doubt about the differentiation between CLL and related conditions a bone marrow sample may be required. Immunophenotyping is essential to differentiate between CLL and certain closely related conditions.

Tests to detect chromosome abnormalities in the leukaemia cells are not part of the routine diagnostic work-up for CLL. They may be done routinely in larger centres or as part of scientific studies of the disease. Although they are not considered essential for diagnosis, they can be important to predict prognosis. Staging in CLL can be done on the basis of blood samples and of physical examination.

How is chronic lymphocytic leukaemia staged?

Staging of CLL is of particular importance in helping to decide when to begin treatment and in estimating likely prognosis and survival. There are two main staging systems used for CLL – these are called the Rai and the Binet system and are summarised in the table below.

Stage	Clinical features	Median survival
Rai 0	Raised numbers of lymphocytes (in blood or marrow)	>10 years
1	As 0 + enlarged nodes	7 years
2	As 0 + enlarged spleen/liver, +/- enlarged nodes	7 years
3	As 0 + anaemia, +/- enlarged nodes, liver or spleen	3-5 years
4	As 0 + low platelets, +/- anaemia, enlarged nodes, liver or spleen	3-5 years
Binet A	Less than three areas of enlarged lymph nodes	>10 years
B	Three or more areas of enlarged lymph nodes	5 years
C	Anaemia +/- low platelets	3-5 years

NB: Median survival is often misunderstood by patients and family to mean the maximum expected lifespan. In fact, it is the time at which one would expect half of a group of patients diagnosed at the same time to still be alive – many of those still alive will live for many more years, decades even. It is also important to realise that not all patients who die after being diagnosed die from CLL. Particularly in the case of elderly patients, many will die from other diseases. Finally, one should always remember that survival data is historical and may not reflect improvements based on newer drugs or treatments.

There is a modified Rai three-stage system that classes stage 0 as low-risk, stages 1 and 2 as intermediate-risk and stages 3 and 4 as high-risk. The modified system is sometimes used in the context of clinical trials.

The Binet system is used more commonly in Europe whereas the Rai system tends to be used in the United States. Although the Binet system does not include a category for a high lymphocyte count in isolation, it is normally possible to compare results of clinical trials even when they do not use the same system.

A condition called smouldering CLL is recognised. These are patients who would be classed as Binet stage A but who have the following features:

- Haemoglobin $>13\text{g/dl}$
- Lymphocyte count $<30 \times 10^9/\text{l}$
- Minimal or no lymph node enlargement
- Non-diffuse pattern of bone marrow disease
- Lymphocyte doubling time >12 months (period in which the number of lymphocytes double in the peripheral blood).

In one study of patients with smouldering CLL, only 15% of patients had shown any progression of the condition after five years and 80% were alive at ten years.



New prognostic markers

Although their exact importance is not yet established several new tests in addition to cytogenetics, are being studied for their potential value in predicting which patients may have more aggressive CLL.

The first of these findings was a rearrangement (mutation) of certain genes (immunoglobulin genes). This mutation occurs in normal antibody producing B lymphocytes when they encounter an antigen³ (this test is called IgVH gene status). Rearranged IgVH genes are thought to indicate relatively mature B cells and are associated with slower disease progression and longer survival. Unmutated IgVH genes (sometimes referred to as germline configuration) are thought to show immaturity of the B cell which seems to be more associated with aggressive disease.

Unfortunately, the test for IgVH status is beyond the capacity of most hospital routine laboratories so this test is not of great value in day-to-day practice.

A marker on the surface of CLL cells called CD38 seems to also have prognostic significance; in this case high levels of CD38 are associated with a poorer outcome; although CD38 results usually correspond with the IgVH gene status results, it is an independent variable. This test is relatively simple but levels of CD38 may vary over the course of the disease requiring repeated sampling. The newest test, for a protein called ZAP-70, is much easier to perform in a routine hospital laboratory. Early results suggest that the ZAP-70 status may be more stable over time than CD38 values. Preliminary results suggest that this may be an important tool in advising patients and in planning treatment; much work remains to be done to confirm the value of ZAP-70.

³ Antigen is a foreign protein which triggers the immune system to mount a response.

How is chronic lymphocytic leukaemia treated?

Principles of treatment⁴

It is generally agreed that, with the possible exception of stem cell transplants for younger patients, there is no curative treatment currently available for CLL. Despite this most patients, happily, will have a long survival and this means that they may well receive a number of different types of treatment during the course of their disease. A significant minority of patients will never require treatment at any time.

For those patients who do require treatment there are three basic aspects of treatment:

- Treatment (if required) of the newly diagnosed patient (standard treatment)
- Treatment of patients with progressive disease or disease resistant to standard treatments
- Treatment of complications, such as infections or autoimmune disease.

⁴ The treatment sections of this booklet are based on guidelines developed by British Committee for Standards in Haematology, part of the British Society for Haematology. The BCSH has a website at www.bcsghguidelines.com. A summary of the guidelines is listed in Appendix A.

Listed below is a brief description of the main drugs used in treatment of patients with CLL.

⌘ Alkylating agents

The most commonly used of these is a drug called chlorambucil; for many years this was the main drug used in treatment of CLL. Another drug of this type called cyclophosphamide may be used with similar effectiveness.

⌘ Anthracyclines

Anthracyclines are drugs commonly used in treatment of leukaemias and lymphomas. They are often used in combination with other drugs.

⌘ Purine analogues⁵

DNA in our cells includes components called purines and pyrimidines. Purine analogues are drugs that are very similar in shape and chemically to natural purines, but when cells try to use them to make DNA they do not fit properly and they stop the process and thus stop the cell from dividing. Lymphocytes, which are the affected cells in CLL, are particularly vulnerable to the effects of purine analogues; the main forms used in treatment of CLL are called fludarabine and cladribine.

⌘ Monoclonal antibodies⁵

A monoclonal antibody is an antibody that has been created in a laboratory and that binds specifically to a component (antigen) present in the membrane of lymphocytes and/or other cells. It is a new kind of treatment that is very different from chemotherapy. Most chemotherapies are chemicals that kill all rapidly dividing cells in the body. A monoclonal antibody is designed to bind to the specific antigen and, with the help of the patient's immune system, this cell is destroyed. The monoclonal antibodies currently being used in treatment of CLL are alemtuzumab (MabCampath), and rituximab (Rituxan).

⁵ Any patient who has been treated with either a purine analogue or monoclonal antibodies should receive irradiated blood products for any future transfusions. This is to prevent a condition called transfusion associated GvHD.

⌘ Steroids

There is no evidence that treatment with steroids combined with the above agents has any benefit in CLL. However, they are important in two situations:

- Patients with Stage C disease should receive a short course of prednisolone before starting chlorambucil. This steroid will improve the blood count which means that chlorambucil will be better tolerated
- To control autoimmune complications.

⌘ Miscellaneous

For patients whose illness does not respond to any of the specific treatments described above, various combinations of the drugs described may be used.

Management of CLL

⌘ Indications for referral

The Department of Health has issued advice to family doctors on when patients should be referred for specialist investigation for possible cancer. For blood cancers the referral indications include:

- A high white count with excessive numbers of lymphocytes (especially in the presence of anaemia or a low platelet count)
- Presence of enlarged lymph nodes or liver/spleen; and
- Symptomatic disease
 - ⌘ weight loss over 10% in last six months
 - ⌘ fever over 38°C for two or more weeks
 - ⌘ extreme fatigue or night sweats.

⚡ Indications for treatment

For many patients with CLL there will be few, if any, periods when they require in-patient treatment for their illness; patients may require inpatient treatment if they develop a severe infection. Patients who have no significant symptoms at the time of diagnosis, and whose laboratory results indicate early stage disease, are likely to be offered check-ups but no treatment – this is often called a ‘watch and wait’ approach.

The criteria suggested in the BCSH guidelines for commencing therapy are:

- Progressive marrow failure: development or worsening of anaemia or low platelets
- Marked (>10cm) or progressive lymph node enlargement
- Marked (>6cm) or progressive enlargement of the spleen
- Progressive lymphocytosis
 - ⚡ 5% increase over two months
 - ⚡ doubling of the lymphocyte count in the blood in less than six months
- Systemic symptoms
 - ⚡ weight loss >10% in last months
 - ⚡ fever >38°C for two or more weeks
 - ⚡ extreme fatigue
 - ⚡ night sweat
 - ⚡ auto-immune haemolytic anaemia or ITP (immune thrombocytopenic purpura).

It is important to rule out other possible causes for these symptoms, such as infection.

Treatment strategy

∴ Initial treatment

Patients with early-stage disease do not require any active treatment.

For patients who do require treatment but who are not candidates for a stem cell transplant entry into CLL4, the current CLL clinical trial,⁶ should be considered. This trial is comparing treatment with either chlorambucil, fludarabine used alone or fludarabine with cyclophosphamide. Chlorambucil is recommended if fludarabine is not advised and a transplant would not be under consideration. Some studies have looked at the use of high doses of chlorambucil, but this is not routinely recommended.

Patients who may be considered for a transplant should receive an initial treatment that is likely to achieve a complete remission, for example, fludarabine. The evidence on use of stem cell transplants for CLL is not conclusive. There is a European study (CLL5) being carried out to determine the ideal timing of a transplant either at completion of initial therapy or after relapse (return of the disease).

Alemtuzumab and rituximab are not recommended as first-line drugs i.e. for previously untreated patients.

∴ Second-line and subsequent therapy

If patients have responded to chlorambucil but then relapsed a further course of chlorambucil may be effective. Patients who do not respond to chlorambucil may be offered fludarabine. For some patients fludarabine is not recommended and in this case CHOP may be used. CHOP is a combination of drugs (cyclophosphamide, doxorubicin, vincristine, prednisolone) widely used for lymphoma (a condition which has many similarities to CLL).

⁶ There is a separate publication on clinical trials available from Leukaemia Research.

If fludarabine has achieved a remission that lasts over a year, any relapse may be effectively treated with fludarabine used alone. If the remission on fludarabine has lasted less than a year then fludarabine may be combined with cyclophosphamide.

There is no generally agreed treatment for patients who do not respond to fludarabine or who respond initially but whose disease becomes resistant to fludarabine. Options include high-dose steroids or monoclonal antibody treatment i.e alemtuzumab or rituximab.

An autologous transplant (using the patient's own stem cells) may be considered for some patients. At present this is only recommended in the context of a trial (currently CLL5). A donor transplant may be considered for a minority of younger, fitter patients; although this is potentially curative it is a relatively high-risk treatment with much greater side-effects than conventional treatments.⁷

Splenectomy may be helpful for patients with a very enlarged spleen which is causing symptoms, or in patients with auto-immune disease. This is discussed below in the section on complications.

Management of complications

∴ Prevention and treatment of infections

Patients with CLL are more prone to serious infections. This is partly because of the disease and partly a result of treatment. This may be a particular problem in elderly patients, those with advanced disease and those receiving active treatment. Most infections are bacterial, with the respiratory system (nose, throat and lungs) being particularly vulnerable. For this reason CLL patients who develop a cough, sore throat or any other sign of infection should consult their GP promptly. If patients have had repeated infections they may be given antibiotics to prevent further infection.

⁷ There is a separate publication on stem cell and bone marrow transplantation available from Leukaemia Research.

All patients being treated with monoclonal antibodies (alemtuzumab or rituximab) will receive special antibiotic cover against an infection called *Pneumocystis carinii*, which may be a problem. This antibiotic cover should continue for at least a further six months after stopping monoclonal antibody treatment.

If patients have very low levels of antibodies (hypogammaglobulinaemia) and repeated infections they may be given intravenous immunoglobulin, especially if antibiotics have failed to prevent infections.

Immunisation tends to be less effective in people with CLL. The specialist will advise the patient on what, if any, vaccinations they should receive. It is recommended that CLL patients should receive annual flu vaccination. However, the effectiveness of this is uncertain and patients should not assume they are protected.

Treatment of minor infections is usually on an outpatient basis but major infections will require treatment in hospital. Because major infections can be life-threatening in CLL patients it is important that patients do not delay seeking medical attention if they suspect they may have an infection.

⚡ Auto-immune cytopenias

Auto-immune conditions are commonly associated with CLL; these may affect blood cells leading to low blood counts (cytopenia). When this affects red cells it leads to auto-immune haemolytic anaemia (AIHA), when it affects platelets it causes a condition known as immune thrombocytopenic purpura (ITP). These conditions may be present at diagnosis or may develop during the illness. Patients who develop AIHA or ITP are treated in the same way as patients with these conditions but who do not have CLL. Presence of AIHA or ITP may influence the choice of other treatments; in particular fludarabine or other purine analogues should not be used in this situation.

∴ Transformation (Richter's syndrome)

CLL can undergo a transformation to a more rapidly progressing condition called chronic lymphocytic leukaemia/prolymphocytic leukaemia. This occurs in around 15% of patients.

Richter's syndrome is the development of a lymphoma in a patient with CLL; it occurs in 5-10% of cases. There is no standard treatment recommendation but it is usually treated in the same way as a high-risk B cell lymphoma.

These two forms tend to respond poorly to treatment and have a poorer prognosis than CLL.

Summary

Chronic lymphocytic leukaemia is a form of cancer which affects blood producing cells in the bone marrow. The disease is unknown in childhood, very uncommon in young people and becomes progressively more common with increasing age. Men are more likely to be affected than women. The majority of patients with CLL have a slowly progressing form with a survival of ten years or more. Chronic lymphocytic leukaemia is not considered curable with the possible exception of younger patients who receive stem cell transplants. A minority of patients have a more rapidly progressing form of the disease with a much shorter median survival.

Standard practice is not to treat patients who have early-stage disease or have no clinical symptoms. There is no evidence that early treatment prolongs survival for these patients. Treatment is started either when patients become symptomatic or when laboratory results indicate that the disease is progressing.

The mainstay of treatment is chemotherapy. In most cases this involves low doses of drugs taken by mouth. The drugs most commonly used are chlorambucil, prednisolone and fludarabine. Radiotherapy has a very limited role in treatment of chronic lymphocytic leukaemia. Most people with CLL would not be considered for a stem cell transplant because of their age and the indolent nature of their disease. For younger patients with rapidly progressing disease a transplant may be curative. There is not yet sufficient evidence to be sure that transplanted patients have achieved cures.

Most patients are able to enjoy a good quality of life for many years, with little or no treatment. For the minority of patients with more rapidly progressing or late-stage disease more intensive therapy may be required. For about 10%-15% of patients the disease will transform into either prolymphocytic leukaemia or into a high-grade non-Hodgkin's lymphoma (Richter's syndrome).

Appendix A

Treatment strategy

✦ Initial treatment

- Treatment of early stage disease is not indicated.
 - ✦ There is clear evidence that patients do not benefit from, and therefore do not require, treatment for early stage CLL. For these patients the recommendation is routine check-ups but no active treatment – this is often called ‘watch and wait’.
- For patients who are not candidates for a transplant entry into the CLL4 clinical trial should be considered.
 - ✦ This trial randomly allocates patients to receive either chlorambucil, fludarabine alone or fludarabine with cyclophosphamide and is considering the value of different prognostic tests and quality of life issues, as well as the outcome of treatment.
- For patients for whom fludarabine is not advised (those with severe renal impairment or autoimmune disease) and for whom a transplant would not be considered, chlorambucil is recommended. (There is no evidence that adding an anthracycline improves survival in this group).
 - ✦ Adding an anthracycline causes more toxicity with no clear benefit.
- There is insufficient evidence to routinely recommend high dose chlorambucil as an initial treatment for CLL.
 - ✦ Some studies have suggested that the outcome may be better with high-dose chlorambucil but these were difficult to compare with standard practice so more evidence is needed before this could be routinely recommended.

- If a patient may be a candidate for a transplant then an initial treatment such as fludarabine which is likely to achieve a complete, or near complete, remission should be chosen. There is no definitive proof of the benefit of an autologous stem cell transplant. There is a European study (CLL-5) that investigates this issue and is offered to patients. In this study patients are randomly allocated to have a transplant immediately after therapy or the procedure is delayed until the disease comes back.
 - ✦ It is important to keep to a minimum the time between fludarabine therapy and collection of stem cells from the blood.
- Alemtuzumab is not recommended for untreated CLL. Rituximab used alone is not recommended for untreated CLL. Rituximab combined with fludarabine (with or without cyclophosphamide) requires further evaluation before it can be routinely recommended.
 - ✦ At present the use of monoclonal antibody-based treatments is reserved for patients who have either relapsed after standard therapy or who did not respond to standard therapy.

✦ **Second-line and subsequent therapy**

- Patients who relapse after having an initial response to low-dose-chlorambucil may be treated with a further course of chlorambucil.
- Patients who do not respond to low-dose chlorambucil may be treated with fludarabine. If patients have severe renal disease or an autoimmune condition they are not recommended to receive fludarabine; these patients should receive CHOP therapy. CHOP is a combination of drugs (cyclophosphamide, doxorubicin vincristine, prednisolone) widely used in treatment of lymphoma and is used (alone or combined with rituximab) in patients with CLL in transformation to Richter's.
- Patients who initially responded to fludarabine, and who experience progression over a year after receiving fludarabine, may be treated again with fludarabine alone.

- Patients who develop progressive disease within one year of receiving fludarabine may be treated with a combination of fludarabine and cyclophosphamide.
- There is no single agreed treatment approach for patients who do not respond to fludarabine or who respond initially but whose disease becomes unresponsive. Options include:
 - ✚ High-dose methyl prednisolone (a steroid), especially for patients with markedly enlarged lymph nodes or with abnormalities of a gene called p53 (or both);
 - ✚ Alemtuzumab is licensed for and recommended in patients who do not have very enlarged lymph nodes and who have previously been treated with alkylating agents and who are not responding to fludarabine;
 - ✚ Rituximab alone is not recommended for previously treated CLL. Rituximab with fludarabine (with or without cyclophosphamide) seems very effective. Further studies are needed to confirm this.
- Autologous transplantation should be considered for patients with a good response to treatment and who are fit enough to withstand high-dose chemotherapy and total body irradiation. Autologous transplantation should be done in the context of a clinical trial such as the CLL 5 trial.
- A donor transplant may be considered for younger, fitter patients who have been previously treated and who have poor risk disease. Suitable patients should be referred at an early stage (to minimise the risk of drug-resistance developing). Although this is considered potentially curative, it is important to stress that the side-effects (short and long term) of this treatment are much greater than for conventional treatments.
- Splenectomy may be of benefit in selected patients who have symptoms caused by a much-enlarged spleen or to improve the blood count in patients with auto-immune disease.

Management of complications

⌚ Prevention and treatment of infections

Infection is a common complication of CLL; this is partly a result of the disease itself and partly a complication of treatment. It results from a number of factors including low levels of antibody (hypogammaglobulinaemia), low numbers of normal white cells (neutropaenia), impaired function of lymphocytes (especially T and NK cell), and defective function of the complement system (a part of the immune response). Infection is a particularly significant danger in the elderly, those with advanced disease and those receiving treatment. There is some evidence that purine analogue treatment may carry a higher risk of infection.

Most infections are bacterial — the respiratory tract (nose, throat and lungs) being especially vulnerable. Blood poisoning (septicaemia), kidney infections, and infections of soft-tissues and the urogenital system are also common. Fungal infections, viral illnesses and infections with normally harmless organisms (opportunistic infections) used to be considered rare but they are being seen more often in patients treated with purine analogues, high-dose steroids and alemtuzumab.

Prevention

○ Antibiotics

- ⌚ Patients who have had repeated chest or urinary infections may be given cycling antibiotic cover (that means prevention by a sequence of different antibiotics taken one after another). There are no large studies to prove whether this works or not — at present it will depend on the judgement of individual doctors whether they use this approach.

- Prophylaxis against *Pneumocystis carinii*
 - ✦ All patients who are receiving purine analogues or alemtuzumab should receive septrin or inhaled pentamidine as a precaution against a respiratory infection called *Pneumocystis carinii* pneumonia. The preventive antibiotics should continue for six months after stopping purine analogues or alemtuzumab.
- Intravenous immunoglobulin
 - ✦ Patients with hypogammaglobulinaemia and recurrent bacterial infections should be given intravenous immunoglobulin, especially if antibiotics have proved ineffective.
- Immunisation
 - ✦ Immunisation is often less effective in patients with CLL than in unaffected people. In particular, there is a poor response to vaccination against diphtheria, typhoid, mumps, influenza, pneumococcus and haemophilus. A special type of vaccine called a conjugated vaccine can sometimes prove more effective for CLL patients and, where such a vaccine is available, it should be used in preference. There is no conjugated form of the flu vaccine.

Although it is standard practice to recommend annual influenza vaccination for CLL patients, the effectiveness is uncertain and patients should not assume they are protected.

Treatment of infections

Patients and carers need to be aware of the special risks of infection and of the need to seek immediate medical attention as soon as the patient suspects they may have an infection. Minor infections can be treated on an outpatient basis but major infections will require treatment in hospital. As infections in CLL patients can be very serious, it is normal to start on broad-spectrum antibiotics as soon as all the essential laboratory samples have been collected.

Autoimmune cytopenias

As mentioned, many patients with CLL develop autoimmune conditions; often these affect the blood cells with the result that patients may become anaemic or have low platelet counts (ITP). Although these conditions may be present at diagnosis, they more usually develop during the illness. There is some evidence that autoimmune haemolytic anaemia (AIHA), which is destruction of red cells by antibodies, is more common after treatment with purine analogues.

It is recommended that patients who do develop AIHA or ITP should be treated in the same way as patients with these conditions who do not have CLL.

Re-treatment with a purine analogue is *not* recommended in a patient who has previously developed AIHA or ITP while receiving a purine analogue. The risk of AIHA in patients with a positive DAT⁸ test but no evidence of red cell destruction is not known. Purine analogues should be used with care in this situation with regular checks of the haemoglobin and the DAT.

Transformation (Richter's syndrome)

Development of lymphoma occurs in 5-10% of patients with CLL; the lymphoma may be present at diagnosis of CLL but most develop during the course of the disease. Special tests have shown that some of the lymphomas have arisen by transformation of CLL cells while others originate from a distinct cell population. Most cases are of the type known as diffuse large B cell lymphoma (DLBCL).

No standard treatment recommendation is made in the guidelines for Richter's transformation of CLL; sufficient evidence is not yet available, but usually these patients are treated as high risk B cell lymphomas. Any patient developing Richter's transformation will have their treatment decided on an individual basis after discussion with his or her doctor.

⁸ DAT (Direct Antiglobulin Test) is a test which detects the presence of antibodies bound to the surface of red cells.

Notes

Notes



Notes



Typical normal values for blood test results

	WBC x 10⁹/l	RBC x 10¹²/l	Hb g/dl	ANC x 10⁹/l	Platelets x 10⁹/l
Adult male	3.7 to 9.5	4.3 to 5.7	13.3 to 16.7	1.7 to 6.1	143 to 332
Adult female	3.9 to 11.1	3.9 to 5.0	11.8 to 14.8	1.7 to 6.1	143 to 332
West Indian	2.8 to 9.8			1.0 to 6.5	122 to 374
African	2.8 to 7.8			0.9 to 4.2	115 to 342
Child 2-5 yrs	5 to 13	4.2 to 5.0	11 to 14	1.5 to 8.5	143 to 332
Child 6-9 yrs	4 to 10	4.3 to 5.1	11 to 14	1.5 to 6.0	143 to 332
Child 9-12 yrs	4 to 10	4.3 to 5.1	11.5 to 15.5	1.5 to 6.0	143 to 332

Normal ranges vary slightly between laboratories so you may wish to ask your doctor to enter your normal values below:

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WBC	White blood cell count
RBC	Red blood cell count
Hb	Haemoglobin concentration
ANC	Absolute neutrophil count

Separate ranges are quoted for West Indian and African populations as these groups have different normal ranges for white cell counts, absolute neutrophil counts and platelet counts.

This information is adapted, with permission, from *A Beginner's Guide to Blood Cells*, Dr Barbara Bain. Pub. Blackwell, Oxford, 1996.

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