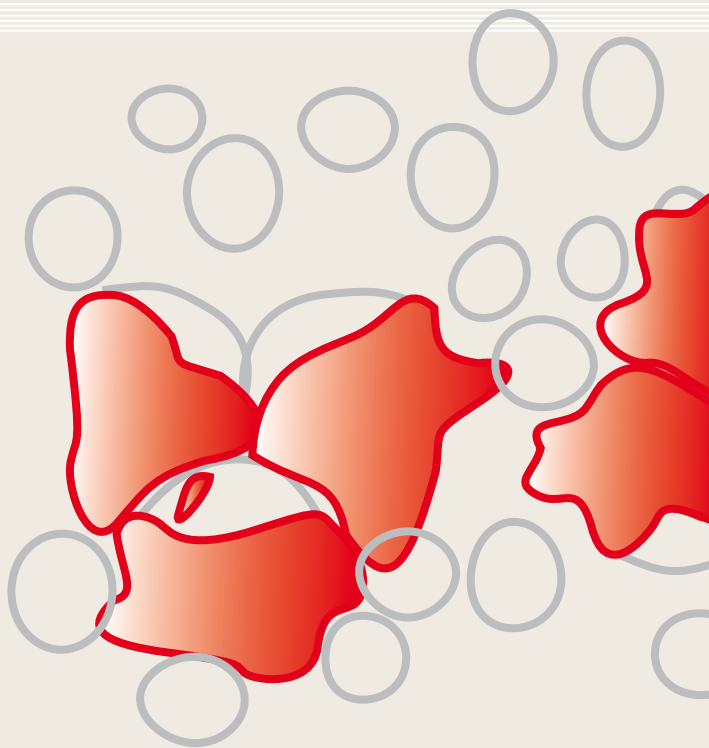


Adult Acute Lymphoblastic Leukaemia (ALL)



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.

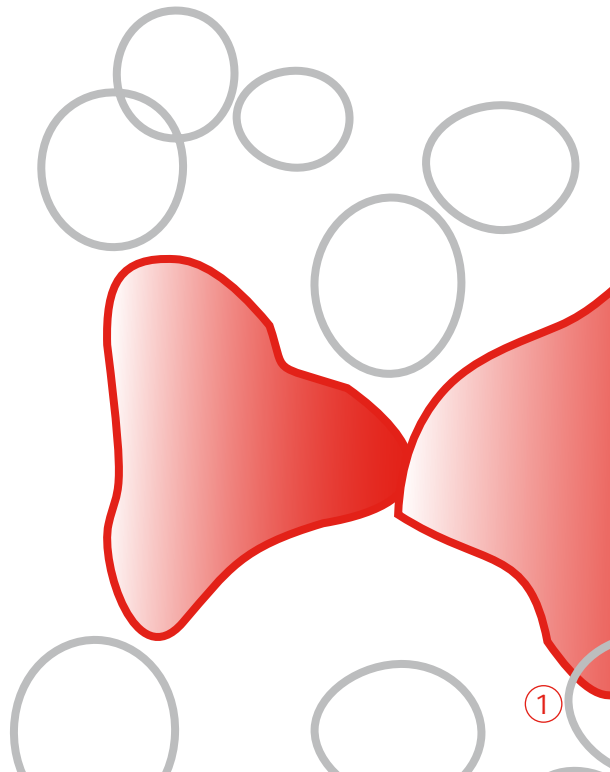
Leukaemia Research
43 Great Ormond Street, London, WC1N 3JJ
020 7405 0101 www.lrf.org.uk
email: info@lrf.org.uk
Registered charity 216032

Series compiled by Ken Campbell, revised 2006. A list of advisors can be found at www.lrf.org.uk/advisors
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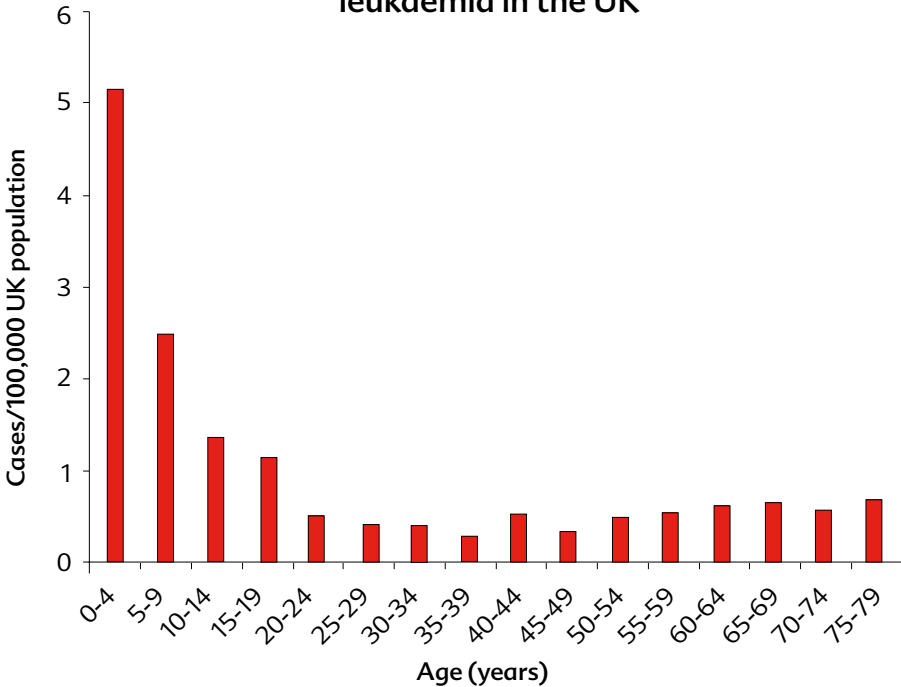
What is acute lymphoblastic leukaemia?

Acute lymphoblastic leukaemia (ALL) is a form of cancer that affects the lymphocytes and lymphocyte-producing cells in the bone marrow. Lymphocytes are white blood cells that produce antibodies and are vital parts of the body's immune system. They can be classified into subgroups according to their function. The two main groups are B cells and T cells. In ALL there is an accumulation of immature lymphocyte-forming cells called blast cells in the bone marrow. Eventually, the production of normal blood cells is affected by this and there is a reduction in the numbers of red cells, white cells and platelets in the blood.



Who gets acute lymphoblastic leukaemia?

Incidence by age of acute lymphoblastic leukaemia in the UK



Acute lymphoblastic leukaemia is the only form of leukaemia that occurs more frequently in children (under 15 years of age) than adults. When it occurs in adults, ALL is most common between the ages of 15 to 25 and in those over 75 years. The disease is slightly more common in males than in females at all ages.

What are the types of acute lymphoblastic leukaemia?

There are two terms used to describe the leukaemia cells in ALL and they are used together rather than as alternatives. They describe different properties of the leukaemia cells.

Immunology

The most important classification system is based on the type of lymphocyte lineage affected, that is the B or T cell. This is known as the immunological classification and is important in planning treatment. The immunological classification together with characterisation of chromosome abnormalities is extremely useful in predicting the response to treatment. Approximately 20% of adult cases of ALL are T cell in origin, 75% are early (precursor) B cell, and 5% are more mature B cell derived. The mature B cell type shows some resemblance to a condition called Burkitt's lymphoma¹ and is therefore sometimes called Burkitt-type ALL. Both T cell ALL and Burkitt-type ALL have many features in common with non-Hodgkin's lymphoma and are treated with similar drug combinations.

Morphology

The other classification system is mainly based on the appearance of the leukaemia cells (morphology) under the microscope. This is described as the FAB classification after the group of French, American and British haematologists who designed the system. It classifies ALL as L1, L2 or L3. This system is not very important clinically because it does not help in planning treatment or predicting outcomes. The majority of adult patients with ALL have the FAB L2 type, which further restricts its clinical significance. L3 is the only clearly distinct type within the FAB system.

¹ A separate publication on Burkitt's lymphoma is available from Leukaemia Research.

What causes acute lymphoblastic leukaemia?

The cause(s) of ALL are unknown in most instances. The only clearly identified risk factor for adults is exposure to very high radiation levels such as those seen after the atom bomb explosions in Japan in 1945. Very few people in the Western world are exposed to high enough levels of radiation to increase the risk of developing leukaemia. Patients who have received chemotherapy or radiotherapy for other forms of cancer show a raised incidence of acute myeloid leukaemia (AML) but not of ALL.

What are the signs and symptoms of acute lymphoblastic leukaemia?

The signs and symptoms seen most often in adult acute lymphoblastic leukaemia are:

- Anaemia (lack of haemoglobin), causing
 - fatigue and limited capacity for exercise
 - breathlessness
- Low platelet counts, causing
 - bruising within the skin
 - bleeding from mucous membranes (e.g. gums) and from the gut
- Low (normal) white cell counts, high numbers of abnormal cells and high metabolic rate, causing
 - persistent infections
 - fever; this is often present even in the absence of clear indications of infection

This group of features is known as the classic triad. Susceptibility to infection is particularly related to low levels of a specific type of white blood cell called the neutrophil. Neutrophil levels are sometimes indicated by the abbreviation – ANC – which stands for absolute neutrophil count. Enlargement of lymph nodes ('glands'), the spleen and the liver may occur together or separately. In T cell ALL enlargement of the lymph nodes within the chest (mediastinum) is common and may be seen on a chest X-ray. This may affect the function of the heart and/or lungs.

How is acute lymphoblastic leukaemia diagnosed?

When a doctor examines a patient with ALL there are no specific signs such as the rashes seen in some infections. Leukaemia is not a clinical diagnosis; it requires the results of laboratory tests to confirm the disease. The following guidelines have been issued by the Department of Health to indicate when GPs should urgently refer patients to a specialist to exclude or confirm the diagnosis of leukaemia:

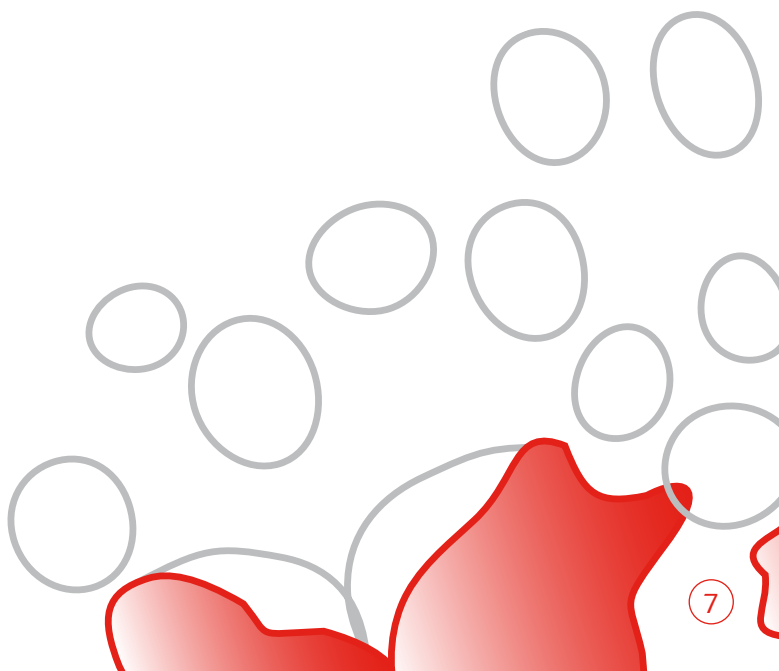
- Blood count/film reported as suggestive of leukaemia²
- Lymphadenopathy (enlarged lymph glands) persisting for six weeks
- Hepatosplenomegaly (enlarged liver or spleen)
- Any three or more of the following symptoms
 - fatigue
 - night sweats
 - weight loss
 - itching
 - breathlessness
 - bruising
 - recurrent infections
 - bone pain

The main laboratory tests used in the diagnosis of leukaemia are a full blood count and, if appropriate, a bone marrow biopsy. Nearly two-thirds of all patients with acute lymphoblastic leukaemia will have a raised white cell count with large numbers of abnormal (malignant) cells.

² If the blood count/film suggests a diagnosis of leukaemia the hospital will usually contact the GP to ask for the patient to be referred.

Even patients with low normal white cell counts will almost always have abnormal cells in the blood. Many patients also have anaemia and/or low platelet counts, because the leukaemia cells actively inhibit production of normal blood cells in the bone marrow. Severe anaemia is observed in 30% of cases and low neutrophil counts are found in 20% of cases.

Chromosome analysis is of great importance in planning the treatment of ALL. This may be done on blood and/or bone marrow samples. Patients with ALL may require X-rays and other imaging procedures (CAT scan, MRI scan) to determine which organs are affected and to what extent. Lumbar puncture (sampling of the fluid around the spine and brain) may be done especially if symptoms suggest involvement of the central nervous system (CNS). About one in twenty patients will have a significant abnormality of the clotting system and so tests for this are routinely included. Various other tests are performed to assess general health, for example heart, liver and kidney function. These are important to identify any patients who might be at particular risk of side-effects from the planned treatment. It may sometimes be necessary to modify the treatment plan, for example, to avoid certain drugs or to reduce the doses.



How is acute lymphoblastic leukaemia treated?

Acute lymphoblastic leukaemia is rapidly fatal without effective treatment. In older or infirm patients who are unable to withstand aggressive treatment doctors may offer palliative care. This form of treatment is intended to improve quality of life without attempting to achieve a cure. In patients who are fit enough to receive aggressive anti-cancer treatment the aim is to achieve a disease-free state called remission and, ultimately, a cure. Treatment normally commences within a few days. Although there is a degree of urgency, it is considered better to wait until all the necessary information is available in order to allow doctors to offer appropriate individual treatment to each patient. Patients with ALL may well be asked to consider taking part in a clinical trial.³

Principles of treatment

There are three phases to treatment of ALL, remission induction, post-remission treatment or consolidation, and an extended period of maintenance treatment. Each of these elements is essential to a successful outcome. Quoted outcomes at various stages of treatment range widely. These ranges represent the results of studies carried out at many centres worldwide. The differences in outcome may be related to the form of treatment given or may mean that groups of patients being treated in different centres are not directly comparable in terms of their original prognosis.

Central nervous system directed therapy

For all risk groups a potential site of relapse is the cerebro-spinal fluid (CSF) surrounding the brain and spinal cord, which usually contains a small number of lymphocytes. Unfortunately, although leukaemia cells can enter the CSF, administration of drugs by mouth or by injection into a vein does not lead to

³ There is a separate publication on clinical trials available from Leukaemia Research.

sufficient accumulation in the fluid. There is therefore a risk that leukaemia cells may survive in this site. For this reason it is normal to give central nervous system directed therapy that starts during remission induction. It involves administration of drugs directly into the CSF by a process called lumbar puncture and is also called intrathecal therapy. Intrathecal therapy is likely to be continued at least until completion of consolidation. In some protocols patients may also receive X-ray treatment to the head (cranial irradiation). In those patients where no cranial irradiation is used intrathecal therapy will continue until the end of maintenance treatment. Patients who receive cranial irradiation may develop a 'somnolence syndrome' some five to seven weeks later. This condition, characterised by nausea, malaise, lethargy and drowsiness, only lasts for a short time and patients fully recover from it.

Treatment planning

A high proportion of patients will achieve remission (clearance of leukaemia cells from blood and bone marrow). Patients are grouped as having standard- or high-risk disease based on the results of the laboratory investigations. Risk in this context refers to the probability of a good long-term outcome for patients given standard treatment. This information is then used to determine which treatment options may be appropriate for a given patient. For patients who fail to respond (this is called refractory ALL) doctors may recommend purely supportive treatment or possibly inclusion in clinical trials. A particularly common form of high-risk adult ALL is known as Philadelphia chromosome positive ALL. This refers to a specific chromosome abnormality rarely observed in childhood ALL but quite common in adult ALL. It is associated with a high-risk of relapse given standard therapy.

The main difference between patients with high- or standard-risk disease is the chance of the patient having a relapse. Remission induction treatment (see below) is the same for all patients and the majority of patients achieve a remission regardless of their risk category. The risk categories are more important in deciding what treatment should be undertaken following remission induction.

Because of the high risk of relapse for patients with poor-risk disease and most patients with standard-risk disease, a stem cell transplant during first remission may be one of the options advised. This will depend partly on the availability of a suitable tissue-matched donor, usually a brother or sister. Patients with very high-risk disease are increasingly being offered stem cell transplantation from an unrelated tissue-matched donor. Stem cell transplantation requires the use of high-dose chemotherapy and/or radiotherapy. For some older patients this may not be an option and alternative strategies may be considered. For patients with particularly low-risk disease a transplant in first remission may not be suggested since the risk of the transplant is likely to be greater than the risk of relapse. This group of patients will normally receive a number of courses of extra treatment following remission induction. This is then followed in some protocols by long-term oral chemotherapy, which takes their treatment duration to a total of two years. This will also be the treatment for many patients without a matched sibling donor in the standard - and even high-risk groups.

∴ Remission induction phase

This involves the use of several drugs in combination to clear all detectable leukaemia cells from the blood and bone marrow. Treatment schedules (protocols) vary but this stage usually lasts between three weeks and two months. Because of the risk of infection and haemorrhage, patients are likely to spend all or most of this stage of treatment as inpatients. The usual combination of drugs used at this stage is vincristine and prednisolone plus an anthracycline (daunorubicin or idarubicin). These combinations can

be expected to achieve remission in over 80% of all patients. A number of protocols also employ cyclophosphamide and asparaginase in order to improve the quality of remissions and affect outcomes in patients with poor-risk disease. It is possible that a drug called Gleevec (formerly called Glivec or STI571) may be of particular value in patients with Philadelphia chromosome positive ALL.

A drug called allopurinol or a drug called Rasburicase will be given to prevent patients developing kidney damage, as a result of the amount of uric acid released when tumour cells are killed. They are normally given as soon as a patient is diagnosed. It is also important for patients to maintain a high fluid intake to reduce the risk of damage to the kidneys. The major side-effects during this period are related to bone marrow suppression. Low neutrophil and platelet counts increase the risk of infection and bleeding respectively. Platelet transfusions can be given to reduce the risk of haemorrhage. Infection must be guarded against by good sterile precautions and prompt treatment must be given if infection occurs. There is some evidence that the use of growth factors to stimulate neutrophil production may reduce the duration and severity of the infection risk. Occasionally, the destruction of cells is so rapid that a condition called tumour-lysis occurs which affects the kidneys. This may require temporary use of an artificial kidney (dialysis). Hair loss is almost inevitable but is temporary.

Consolidation

This is sometimes referred to as post-induction or post-remission therapy. Disappearance of leukaemia cells from the blood and bone marrow does not mean that all the leukaemia cells in the body have been killed. In order to optimise the outcome of treatment it is necessary to give further courses (called blocks) of treatment soon after completion of remission induction. The number of blocks of treatment and the exact drug combinations used vary between clinical protocols. Typically the same drugs used for remission induction will be used again with the addition of cytosine arabinoside,

etoposide, thioguanine or methotrexate. This stage of treatment typically lasts for several months on an outpatient basis but may also require one or more inpatient stays. The drugs used are alternated to reduce the likelihood of leukaemia cells developing resistance to them. Sensitive tests have been developed to detect leukaemia cells that may still be present in the bone marrow after remission induction. These tests may in the future help in planning therapy in individual patients depending on whether or not this 'minimal residual disease' can be detected at different time points throughout treatment.

∴ Maintenance

This phase is unique to the treatment of acute lymphoblastic leukaemia. It has been shown that extended low-dosage oral chemotherapy is essential to reduce the risk of late relapses in patients who appear to be in full remission. The exact reasons for this requirement are not known but it is clear from a number of studies that omitting this phase of treatment leads to significantly worse results. In adults, maintenance therapy typically extends to two years from the time that treatment starts and can usually be completed on an outpatient basis. Patients rarely need hospital admission unless they experience a relapse or develop an infection. The drugs most commonly used are prednisolone, mercaptopurine and methotrexate by mouth and vincristine by injection.

Stem cell transplantation⁴

Stem cell transplantation (SCT) is the term now used in place of bone marrow transplantation (BMT). A bone marrow transplant is one form of SCT but for an increasing number of patients stem cells are now being collected by a machine from the circulating blood. A transplant may be carried out using cells from the patient or from related or unrelated donors. An allogeneic transplant uses cells from a donor whereas an autologous transplant uses the patient's own stem cells. For an allogeneic transplant the preferred donor,

⁴ There is a separate publication on stem cell transplantation available from Leukaemia Research.

where available, is a sibling with a closely matched tissue type. If a related donor is not available an unrelated donor from a volunteer panel may be considered. Allogeneic transplants offer a better chance of eliminating the leukaemia but they also carry a higher risk of graft rejection and of a condition called graft versus host disease (GvHD). The risks of both events are even greater with an unrelated donor. Autologous transplants are less inherently risky in terms of graft failure or graft versus host disease, because patients are receiving their own stem cells. There is, however, a greater risk of return of the original leukaemia if it has not been eradicated completely from the bone marrow or stem cell harvest.

The European Group for Blood and Marrow Transplantation has produced a handbook with recommendations for the use of stem cell transplants. The handbook indicates that stem cell transplants may be considered for high or standard-risk adult ALL patients in first complete remission if they have a matched sibling donor. If they have no such donor then an autologous transplant may be performed in the context of a clinical trial. Patients who suffer a relapse but succeed in achieving a second remission should have a stem cell transplant if a tissue-matched donor can be found. Patients who fail to achieve a remission after two cycles of induction therapy should be considered for a sibling donor transplant. If a sibling donor is not available they may be considered for a matched unrelated donor transplant, provided such a donor can be found quickly enough.

Treatment of relapse

Unfortunately, although as many as eight out of ten adults with ALL will achieve a remission this does not necessarily mean that they are cured. Many patients will relapse, which means that their disease will return. Relapse often occurs because the leukaemia cells have become resistant to drug treatment. This drug resistance is often not specific to a particular drug. It may affect all, or virtually all anti-leukaemia drugs and this is known as multi-drug resistance

(MDR). A number of drugs are being studied which may prevent or reverse MDR. It is because of drug resistance that the overall cure rate for adult ALL varies between 20 and 40%.

The first step in treating relapsed ALL is a repeat of the remission induction programme. This may involve an increased intensity of treatment compared with the original course. Various studies have shown success rates for second remission induction varying between 40 and 75%. Because second remissions tend to be short it is normal at this stage to seek a matched donor for a possible stem cell transplant. Patients who relapse and who do not have a donor available may be invited to consider an autologous transplant within a clinical trial setting. Alternatively, they may be invited to consider entry into a clinical trial to test novel treatment options for relapsed disease. Some patients at this stage may choose to receive purely palliative therapy.

Acute lymphoblastic leukaemia in patients over 60 years

In patients who are over 60 when they are diagnosed with ALL it is more difficult to obtain a remission and relapse is more common. This chiefly relates to the high incidence of Philadelphia chromosome positive disease and to the problems of giving full dose therapy to older patients. In this age group patients may well have other medical problems and they may not be able to withstand the high doses of treatment. It is well established that any significant reduction in dose will reduce the chance of a successful outcome.

Follow-up

The main purposes of follow-up of patients treated for ALL are detection of relapse and treatment complications. During the extended maintenance phase of treatment it is usual to monitor patients every two to three weeks on an outpatient basis. During the first year following completion of chemotherapy patients are normally checked every two to three months. Checks will then gradually become less frequent and are arranged annually at five years and beyond.

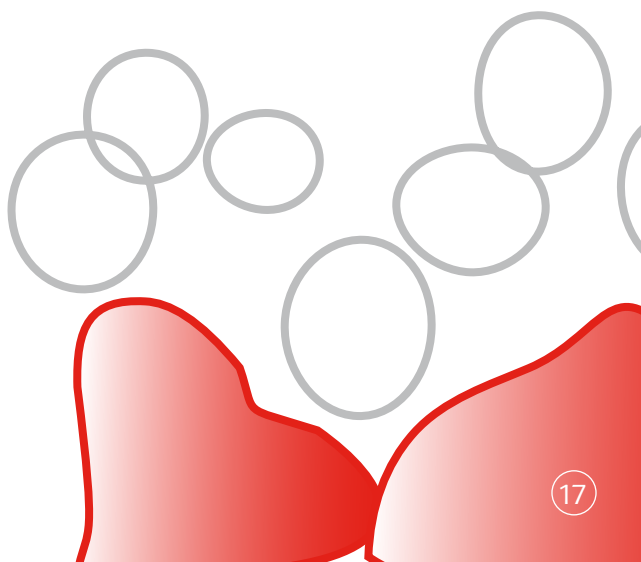
In comparison to childhood ALL there is comparatively little data on the long-term effects of treatment for adult ALL. This is chiefly because of the relatively small number of patients available for study. Secondary cancers are recognised, although thankfully uncommon, consequence of drug and radiation therapy for childhood ALL. In adults, once again, there is much less data available on the frequency of this complication. It is tempting to assume that the risk of complications developing in adults will be similar to that in children, but this is not necessarily true because there are important differences in the biological features of ALL in adults and children. Patients should discuss any concerns about possible long-term effects of treatment with their specialist.

It is important that patients attend maintenance follow-up clinics regularly because it may be necessary for drug doses to be adjusted. Where a patient has been referred to a specialist centre for treatment it is usually possible to arrange for blood tests to be done at a local hospital if this is more convenient. When a patient is in complete remission and has had all the initial treatment their lifestyle can return to normal in almost every way. Patients can resume work and other regular activities. Food and alcohol intake (within moderation) can return to how they were before the leukaemia was diagnosed. At this stage the patient will still be continuing on maintenance chemotherapy. Patients need not normally be admitted to hospital unless they relapse or

develop a severe infection. If a member of the family develops an infection it would be wise to check with the care team whether any special precautions are necessary.

Sexual relations should return to normal. The doctor will discuss with patients, and their partners if appropriate, the likely effects of treatment on fertility. A significant concern for young patients is the likelihood of becoming infertile. Sometimes a patient who has been treated for leukaemia will worry that if they do have children their child will be at higher risk of cancer or other defects because of the treatment. Studies have shown that there is no increased risk of an abnormality or malignancy in children of former cancer patients. The doctor will be happy to discuss a patient's intentions to begin or increase a family.

Patients are free to travel and go on holiday. A patient who has received chemotherapy treatment can receive the normal inoculations that may be necessary for foreign travel and should discuss this with their specialist. However, a patient who has had any form of stem cell transplant should not have a vaccination or inoculation without checking with the specialist responsible for the transplant. Any patient who requires medical care at any time by a doctor other than their GP or specialist should tell the doctor that they are currently being treated for leukaemia and they should give contact details of their specialist.



Prognosis

As discussed in the treatment sections, most patients can expect to achieve a good first remission. The major factors affecting the outcome of treatment at this point appear to be age and white blood cell count at the time of diagnosis. Achievement of complete remission is most likely in younger patients with moderately increased white blood cell counts. Broadly, it is expected that about 70-85% of patients will achieve a successful first remission and overall cure rates are reported as varying between 20-40%. Prognosis varies between different sub-types of the disease and according to risk factors such as chromosome abnormalities (cytogenetics). The only reliable source of advice on prognosis is the specialist who has been treating the individual patient.

Summary

Adult acute lymphoblastic leukaemia is a form of cancer affecting blood producing cells in the bone marrow. Although adult ALL is a very serious disease which is almost uniformly fatal if not treated, it is potentially curable with standard chemotherapy, with or without stem cell transplantation. About eight out of ten patients will achieve a remission but overall cure rates are between 20-40%. The difference between the number of patients who achieve remission and those who are cured is mainly due to those patients who experience relapse of their original disease.

Treatment is based on the use of drugs in various combinations. There are three phases to treatment of adult ALL. The initial phase is called remission induction and uses relatively high drug doses to rapidly reduce the number of leukaemia cells in the body. This phase typically lasts between three and eight weeks on an inpatient basis. Consolidation therapy is intended to further reduce the number of leukaemia cells in the body and this treatment may last for several months. Treatment to the central nervous system is given as intrathecal chemotherapy, with or without cranial irradiation. Finally, and uniquely to this form of leukaemia, there is a maintenance phase extending to two years from the time of diagnosis during which patients take low doses of drugs as outpatients.

Stem cell transplantation is not used routinely in the treatment of adult ALL. It may be, however, appropriate for a high proportion of the patients thought to be at high risk of relapse, or for patients who have experienced relapse but have achieved a second remission.

The prognosis for adult ALL varies depending in part on characteristics of the patient such as age and other medical problems and in part on the features of their disease. Each patient should seek individual advice on their prognosis from their specialist.

Notes



Typical normal values for blood test results

	WBC x 10 ⁹ /l	RBC x 10 ¹² /l	Hb g/dl	ANC x 10 ⁹ /l	Platelets x 10 ⁹ /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.

The following patient information booklets are available free of charge from Leukaemia Research. You can download them from our website or request copies by phone or post (see form inside):

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Acute Promyelocytic Leukaemia

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Childhood Acute Lymphoblastic Leukaemia (ALL)

Childhood Acute Myeloid Leukaemia (AML)

Chronic Lymphocytic Leukaemia (CLL)

Chronic Myeloid Leukaemia (CML)

Hodgkin's Lymphoma (HL)

Multiple Myeloma (MM)

Non-Hodgkin's Lymphoma (NHL)

The Myelodysplastic Syndromes (MDS)

The Myeloproliferative Disorders (MPD)

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Donating stem cells – what's involved?

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Leukaemia Research, 43 Great Ormond Street, London, WC1N 3JJ

T: 020 7405 0101 • F: 020 7405 3139 • E: info@lrf.org.uk

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