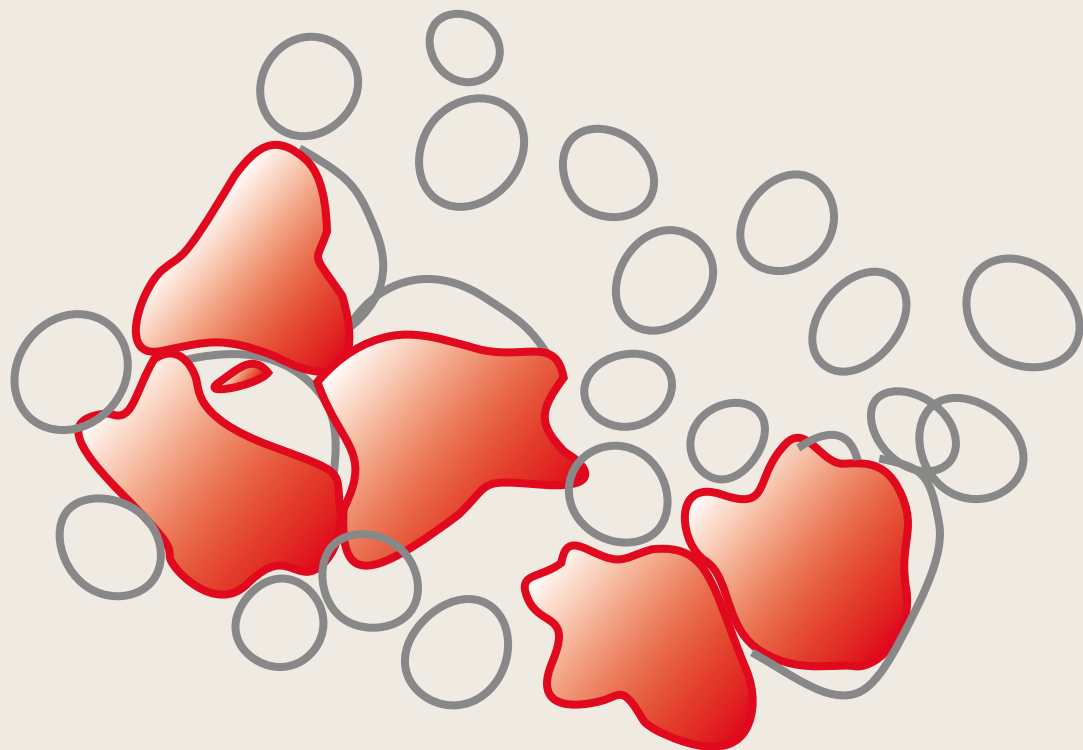


Adult Acute Myeloid Leukaemia (AML)



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 topics 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 acute myeloid leukaemia?

Acute Myeloid Leukaemia (AML)¹ is a form of cancer that affects the cells producing myeloid blood cells in the bone marrow. Myeloid cells are red blood cells, platelets and all white cells except lymphocytes. Almost all cases of AML affect those cells in the bone marrow which produce white blood cells. More rarely AML may affect other cells in the bone marrow which produce red blood cells or platelets.

Non-lymphocytic white cells include:

- Neutrophils – which mainly combat bacterial infection
- Monocytes – which destroy more resistant bacteria, also give rise to tissue immune cells called macrophages, and are essential for effective function of antibody producing lymphocytes
- Eosinophils – which are important to defend against parasites and are involved in allergic reactions
- Basophils – which are also involved in allergic reactions and form part of the non-specific defences triggered by local tissue damage

In acute myeloid leukaemia the abnormal cells are white blood cells of the myeloid type. Immature cells known as ‘blast cells’ accumulate in the bone marrow. The blast cells are unable to mature (differentiate) properly leading to a significant reduction of normal white blood cells in the circulation. The accumulation of blast cells in the marrow also prevents production of other cell types resulting in anaemia and low platelet counts. Blast cells tend to spill-over into the bloodstream which is when they can be picked up by a blood test. The types of acute myeloid leukaemia that predominantly affect red cell or platelet producing cells in the bone marrow are known as erythroleukaemia and acute megakaryocytic leukaemia respectively.

¹Acute myeloid leukaemia (AML) is sometimes referred to as acute non-lymphocytic leukaemia (ANLL), especially in American publications.

About 10% of all cases of AML are of a specific sub-type known as acute promyelocytic leukaemia (APL); there are major differences in the way this form of the disease is treated which are not discussed in this booklet. There is a separate booklet on APL available from Leukaemia Research.

What are the types of acute myeloid leukaemia?

The system presently most widely used to classify AML was developed by the World Health Organization and is called the WHO classification. This is based on an earlier, simpler system called the FAB classification. The FAB and WHO systems are described in detail in Appendix One. An initial report is sometimes based on the FAB criteria because this can be more rapidly assessed. After treatment has begun, the sub-type will be reviewed on the basis of the definitive WHO classification. In most cases, there is no need to modify treatment; occasionally a patient's risk category may be reviewed on the basis of the more detailed classification.

Chromosome analysis (cytogenetics) is of considerable importance in the diagnosis and treatment planning of adult AML. The analysis is usually done on a bone marrow sample. Detailed examination of chromosomes from leukaemic cells shows distinctive abnormalities in almost all cases. The commonest type of change is called a translocation and involves exchange of genetic material between two chromosomes. The study of these changes is of particular importance in identifying the sub-type of AML.² The implications of such changes are discussed below in the section on treatment planning.

There are four main groups within the WHO classification:

- AML with recurrent genetic abnormalities
 - ✦ The leukaemia cells have characteristic chromosomal abnormalities (typically exchanges of genetic material called translocations). These abnormalities tend to predict how the disease will respond to treatment.

²Usually APL can be recognized from the blood film but occasionally it can only be diagnosed when the cytogenetic test results are available. This distinction is important because APL is treated differently.

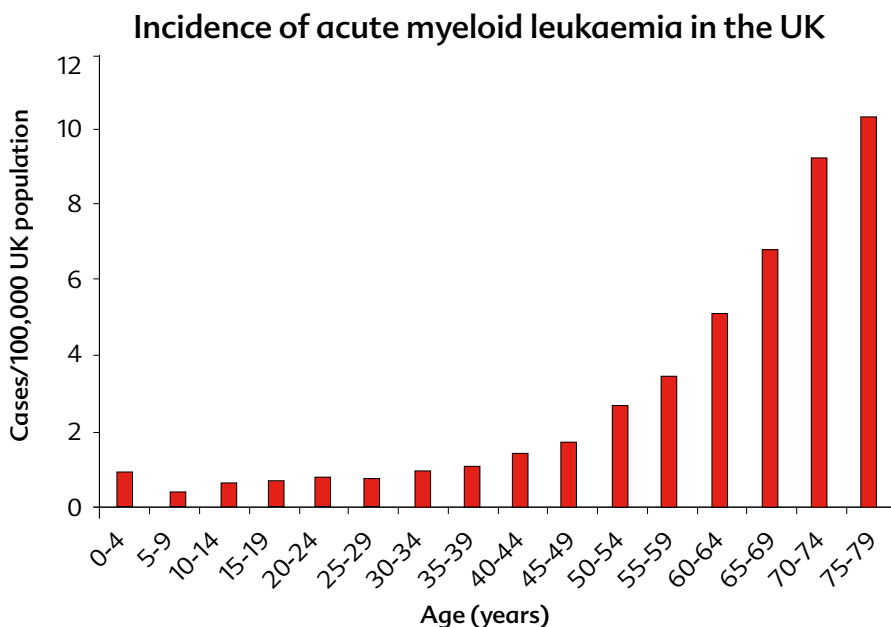
- AML with multilineage dysplasia
 - ❖ In this form of the disease several different types of myeloid cells are affected, often including the platelet-forming cells (megakaryocytes). Sub-groups depend on whether the patient had previously been diagnosed with myelodysplastic syndrome (MDS)
- AML therapy related (tAML)
 - ❖ This group includes patients who develop AML having previously received treatment with chemotherapy or radiotherapy
- Other
 - ❖ All cases which do not fit the previous three groups are included in this category



Who gets acute myeloid leukaemia?

The incidence is slightly higher in males than in females. Acute myeloid leukaemia affects all ages but the incidence rises progressively above the age of 40 years. The average age of onset is about 65 years, and about two-thirds of all patients are aged over 60 at the time of diagnosis. Only about 25% of cases occur in people under the age of 25 years.

There are important differences in the recommended management of AML in older and younger patients – and these are discussed within the treatment section.³



³This booklet does not discuss treatment of children with AML, there is a separate Leukaemia Research booklet on childhood AML.

What causes acute myeloid leukaemia?

The cause(s) of AML are unknown in most instances. One clearly identified risk factor is exposure to very high radiation levels such as those seen after the atom bomb explosions in Japan in 1945. However, very few people in the Western world are exposed to levels of radiation high enough to increase the risk of leukaemia. An exception may be patients who have received radiotherapy for treatment of cancer.

Certain chemical exposures have been clearly shown to increase the risk of AML. Cigarette smoking has been reported to increase the risk of developing adult AML. The amount of benzene in cigarette smoke is thought to be enough to account for this increased risk. Benzene exposure from exhaust fumes is typically far lower than the level known to cause leukaemia.

The use of certain types of chemotherapy or radiotherapy for treatment of cancer increases the risk of developing AML. Depending on the original treatment received the risk of developing AML is most significant between one and ten years post-treatment. This form is referred to as treatment related AML (tAML). It should be stressed this affects only a very small percentage of patients in this situation.

Certain conditions affecting the bone marrow are associated with a significant risk of developing AML. This is particularly true in older patients over about 60 years of age. In this group it may account for as many as 25-40% of cases. The conditions that are associated with secondary AML are often referred to as antecedent haematological disorders (AHD) and include:

Myelodysplastic syndromes (MDS)⁴

- Refractory anaemia
- Refractory anaemia with ring sideroblasts
- Refractory anaemia with excess blasts
- Refractory anaemia with excess blasts in transformation
- Chronic myelomonocytic leukaemia

Myeloproliferative disorders (MPD)⁴

- Essential thrombocythaemia
- Polycythaemia rubra vera
- Myelofibrosis

Both tAML and secondary AML tend to be associated with resistance to standard chemotherapy and they have a poorer overall prognosis compared with primary (de-novo) AML.

⁴There are separate booklets on the Myelodysplastic Syndromes and the Myeloproliferative Disorders available from Leukaemia Research

What are the signs and symptoms of acute myeloid leukaemia?

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

- Anaemia (lack of haemoglobin), causing
 - ✦ Fatigue and limited capacity for exercise
 - ✦ Breathlessness on exertion
- Low platelet counts, causing
 - ✦ Bruising within the skin
 - ✦ Bleeding from mucous membranes e.g. gums, from wounds or 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 — fatigue, bleeding/bruising and infection/fever — may be referred to as the classic triad when they are seen together. When first seen by a doctor almost all patients with AML will have at least one of these characteristic features and half of all patients will show the classic triad.

Less frequently, symptoms of AML may relate to leukaemia cells infiltrating other tissues. Examples of this include bone pain, enlarged lymph nodes (glands), enlarged liver or spleen, involvement of the central nervous system and chloromas (masses of leukaemic cells, often within the skin). Chloromas are rare, affecting less than 5% of patients. Very rarely a chloroma may be present without evidence of leukaemia in the bone marrow or blood. Such patients have a very high probability of leukaemia soon after the chloroma develops.

Bleeding (sometimes severe) may occur. Swelling of the gums and enlargement of liver, spleen or lymph nodes or skin involvement are seen in some patients. Rarely, a very high white cell count can be associated with central nervous system involvement and a condition called leukostasis, in which blood flow is slowed and even locally blocked by large numbers of leukaemia cells.



How is acute myeloid leukaemia diagnosed?

Leukaemia is not a clinical diagnosis – it may be suspected clinically but requires confirmation based on the results of laboratory tests.

When a doctor examines a patient with AML there are often no specific signs or symptoms. The presence of characteristic gum swelling or of soft tissue swellings called chloroma may be strongly suggestive of AML but is not sufficient to make a diagnosis without confirmation by laboratory tests.

The main laboratory tests used in the diagnosis of leukaemia are a full blood count and a bone marrow biopsy. It is recommended that bone marrow samples should be taken from all patients with suspected AML. This involves obtaining a small amount of marrow from inside the bone with a needle (aspirate) and usually a sample from the bone itself to show the structure of the bone marrow cavity (trephine). The samples are usually obtained from the back of the hipbone. The sternum (breastbone) may occasionally be used for bone marrow aspirates (but not for trephines). The procedure causes some discomfort but does not take very long. The procedure is carried out with a local anaesthetic and if necessary sedation may be given beforehand. A patient will not usually have a bone marrow sample taken if there is a very high number of leukaemia cells in their blood at diagnosis and if intensive treatment is not being recommended.

Most patients with AML have a low white cell count but abnormal cells are almost always present in the blood at diagnosis. The bone marrow, in contrast, always contains significant numbers of abnormal cells. In the minority of cases where the white cell count is raised, this is usually due to the presence of abnormal AML cells in the blood that have escaped from the bone marrow. It is a part of the definition of AML that the number of blasts in the bone marrow is greater than 20% of the total number of cells.

Many patients also have low red cell counts (anaemia) and/or low platelet counts. This happens because the leukaemia cells both crowd-out and actively inhibit production of normal blood cells in the bone marrow. The red cell and platelet counts vary from normal to very low levels. All blood films are stained using standard dyes which allow laboratory staff and doctors to identify different types of blood cells.

A technique known as immunophenotyping, which detects markers either on the surface or within the cell, is very useful for identifying and classifying the sub-types of AML. The results of this test may be important for deciding treatment. Some newer treatments are only effective against AML cells carrying certain specific markers, thus the results of immunophenotyping are particularly important in considering these treatments.

Lumbar puncture is the insertion of a needle into the space around the spine; this allows sampling of the cerebro-spinal fluid (CSF), which surrounds and cushions the spine and brain. Leukaemia cells may sometimes be present in the CSF. Drugs administered in standard dose, intravenously or by mouth, do not enter this fluid and so leukaemia cells can survive in the CSF. Certain types of AML are more likely to have CNS involvement and only patients with these forms of AML have routine lumbar punctures. Lumbar puncture is only done on other patients if symptoms suggest that the nervous system may be affected.

Tests of the clotting system are routinely done on all patients with AML because this will help to detect unrecognised cases of the APL variant which requires different management. Various other tests are performed to assess general health, for example heart, liver and kidney function. A general assessment of the patient's health is important to identify those patients who may be particularly vulnerable to side effects from treatment.

How is acute myeloid leukaemia treated?

The treatment section⁵ of this booklet is based on the British Committee for Standards in Haematology Guidelines for Management of Acute Myeloid Leukaemia in Adults the latest version of which can be found on the web at www.bcshguidelines.com/pdf/AML_230505.pdf

General measures and supportive care⁶

There has been a steady improvement in survival for AML patients over the last 30 years. Although there have been advances in chemotherapy, most of this improvement in survival has occurred because of better prevention and management of problems such as infection and anaemia. This in turn has allowed patients to receive increased intensity of treatment. Age is one of the strongest predictors of fitness for treatment; this is not the only factor however and a young patient with other medical problems may be less suitable for intensive therapy than a very fit, but much older, patient. A particular problem with older patients is that they often cannot tolerate full doses of chemotherapy, and this accounts in part for their poorer prognosis.

There are still many unanswered questions about the best way to treat the disease. For this reason, patients are usually asked to consider taking part in a clinical study (trial), which is a scientific comparison of two or more possible treatment options. AML studies currently have three main aims; to reduce the number of patients who relapse, to improve the management of relapsed disease and to minimise the impact of side effects on those who are successfully treated for adult AML. The safety and well being of the patient is always the first priority in any study.

⁵Treatment of a sub-type of AML called acute promyelocytic leukaemia (APL) is not discussed in this booklet. A separate booklet on this condition is available from Leukaemia Research.

⁶There is a separate booklet on the supportive care of patients with blood cancer available from Leukaemia Research.

Clinical studies normally compare newer drugs or new ways of using existing drugs with the best currently available treatment(s). Patients are advised to ask about clinical studies available at the treatment centre.

Palliative care teams may be involved at an early stage to offer support to patients and family members.

Treatment planning

The most important factors in treatment planning are:

- Whether the patient is fit and well enough to receive intensive chemotherapy (and wishes to do so) and
- Whether doctors think there is a high risk that AML will return (a relapse) following standard treatment

As stated above, age is one of the strongest predictors of fitness for treatment; this is not the only factor however and a young patient with other medical problems may be less suitable for intensive therapy than a very fit, but much older, patient.

The risk of a relapse is estimated on the basis of the cytogenetic test results, which are available soon after diagnosis, and of the response to the first course of treatment. Risk factors are discussed in more detail in Appendix Two. Some patients will be classified as having poor-risk disease soon after diagnosis; others will initially be classed as better risk but then re-classified as poor risk on the basis of their response to treatment.

Patients who are already known to be at high risk of relapse, based on test results, will be asked at an early stage to consider entering a study. For other patients, treatment decisions will be reviewed after the first course of treatment. Patients who do not show a marked reduction in the number of leukaemia cells, at this point, are unlikely to respond well to standard treatment and may be asked to consider entering into a study.

All patients should be fully informed of both the advantages and disadvantages of all available treatments and of the strategies that can be used to treat long-term side effects.

Phases of treatment

There are two phases to treatment of AML, remission induction followed by consolidation therapy.

Induction therapy is intended to clear leukaemia cells from the blood and marrow (remission). The aim of this phase is to rapidly restore normal bone marrow function. A complete remission is defined as recovery of normal production of blood cells by the marrow with fewer than 5% blast (primitive) cells in the marrow and no evidence of a cytogenetic (chromosome) abnormality.

Treatment may be defined as intensive or non-intensive, depending on the amounts of chemotherapy given and the timing of treatment blocks. Intensive therapy offers the possibility of cure, or at least of a long-lasting remission,

but involves more severe treatment side effects. Most intensive treatment programmes (regimens) involve four or five courses of chemotherapy. Non-intensive treatment usually involves the use of the same drugs but in lower doses and with fewer courses of chemotherapy. This offers less chance of a sustained remission but is much less toxic and so may be better for older patients or those with other medical problems.

Anthracyclines are drugs that bind to DNA and damage its structure; this is particularly effective against rapidly dividing cells. A drawback of this group of drugs is the risk of heart damage which may limit their use, especially in older patients. The likelihood and severity of heart damage depends on the total amount of anthracyclines received; this may cause particular problems for patients who relapse and require further treatment. Some of the more commonly used examples are daunorubicin, doxorubicin and the newer idarubicin and mitoxantrone. Recent studies have shown no additional benefit from using the newer drugs compared to daunorubicin and so daunorubicin is widely used in treatment of AML.

Like anthracyclines, a drug called cytarabine stops cells from dividing; this is because it resembles one of the components of DNA but cannot be used by the cell to make working DNA. Cytarabine does not carry the same risks of heart damage as anthracyclines.

Initial treatment usually uses a combination of an anthracycline (or anthracycline-like drug) and cytarabine. Some patients will receive additional treatment to prevent the disease from relapsing in the central nervous system. This is discussed in detail in Appendix Three.

The recommendations for management are:

- All patients who are eligible for a trial should be asked to consider this option. The clinician will select which trial is appropriate for the patient and provide detailed information.

- Patients who are unwilling to enter a trial, or for whom there is no trial available, should receive standard daunorubicin and cytarabine induction chemotherapy.
- Patients who choose to receive non-intensive chemotherapy (and do not enter a trial) should be treated with low dose cytarabine. This can often be given as an out-patient.
- Patients who are not well enough to receive chemotherapy should receive best supportive care; usually this will mean transfusion support and possibly low doses of a drug called hydroxyurea (hydroxycarbamide) to control the white cell count. Hydroxyurea has fewer and less severe side effects than other drugs, especially when used in low doses.

✦ **Consolidation therapy**

Remission induction is followed by consolidation therapy to reduce the risk of relapse. Unless patients receive further therapy relapse is likely to occur within one year. To prevent this further treatment is given; this is often referred to as consolidation. Consolidation chemotherapy sometimes uses the same drugs as remission induction, but different drugs are often used to minimize the risk that the disease will become drug resistant. Consolidation therapy will consist of further courses of chemotherapy which may be followed by a stem cell transplant from a donor. The role of autografting (transplants which use a patient's own stored stem cells) in the management of AML is contentious and it is not routinely offered.⁷

The use of more intensive consolidation chemotherapy appears to improve outcomes but it is not yet clear which drugs are best for this or how they should be given. The current UK clinical trial (AML 15) is comparing a number of different drug combinations, with or without addition of a targeted treatment called gemtuzumab ozogomycin (Mylotarg™). Mylotarg™ is a monoclonal antibody (a very pure antibody which binds only to leukaemia

⁷There is a separate booklet available from Leukaemia Research which discusses Stem Cell and Bone Marrow Transplantation.

cells), which is combined with a very powerful drug which is released only when the antibody encounters a target cell.

The drug used is so toxic that side effects would be intolerable if the drug were not accurately targeted at the leukaemia cells.

Standard or poor risk patients who have a matched sibling donor are typically offered the option of a stem cell transplant after the second course of chemotherapy. Stem cell transplantation has the potential to achieve long-term disease free survival in some patients; however, the side effects of a transplant are greater than those for conventional chemotherapy treatment and many patients are not fit enough to tolerate this treatment or lack a donor. All patients of childbearing years undergoing stem cell transplants should ask about options to preserve their fertility before treatment (see section on long-term effects of treatment).

The recommendations for use of chemotherapy or stem cell transplants (SCT) as consolidation are summarized below.

- Patients who have achieved a remission and who have good risk disease or who are unwilling to consider a transplant should receive intensive chemotherapy as consolidation. A transplant remains a possible option for these patients if they should have a relapse.
- Patients with high risk AML (as defined in Appendix Two), who achieve a remission and who have a well-matched donor may be offered a donor (allogeneic) transplant; it is accepted, however, that only a minority of patients will benefit from this.

- Standard risk patients in remission are only likely to be offered a donor transplant as part of a clinical trial.
- Allogeneic (donor) transplantation may be the treatment of choice for younger patients who are in second remission; in other words patients who have relapsed but then achieve a second remission with further treatment.
- Older patients, with high risk disease or who have relapsed following a remission, may be offered a reduced intensity transplant if there is a clinical trial available which includes this as an option.
- Younger high-risk patients or those who have had one or more relapses may be considered for a haplo-identical transplant, but only within a clinical trial (a haplo-identical transplant is one from a relative who is 'half-matched' to the patient, not fully matched).

✧ **Treatment of relapse**

Unfortunately, relapse is common in AML and may affect half or more of all patients who achieve a remission. Although some patients who relapse will respond well to re-treatment, many will not. There are features of the leukaemia cells, and of the results of initial treatment, that help specialists to predict the likely chances of successful re-treatment. If the doctors feel that re-treatment is unlikely to succeed patients may be advised that palliative care is more appropriate than intensive therapy. Palliative care is designed to alleviate symptoms and control the disease rather than attempting to achieve a cure. If the doctors feel that palliative care may be more appropriate they will discuss the options in detail before a treatment plan is decided. It is important to emphasize that palliative care is not synonymous with terminal care; treatment of patients in this situation will seek to extend survival as well as controlling symptoms.

Patients who do achieve a second remission and who are eligible may be considered for a stem cell transplant. It is important to stress that, for many patients with AML, their age and/or general health may mean that a transplant is deemed unacceptably dangerous.

AML in patients over 60 years

About two-thirds of all patients in the UK with AML are aged sixty or over at the time of diagnosis. These older patients are much more likely to have underlying, often undiagnosed, problems affecting other systems; for example around seven out of ten people over the age of 60 have cardiovascular disease compared to only around one in ten of those under 60.

In addition, high-risk disease and secondary leukaemia are more frequently seen in patients in this age group. These patients are more likely to develop resistance to standard anti-leukaemia drugs. Serious infectious complications as a result of the disease and its treatment are more common. Older patients are often unable to tolerate the full doses of drugs that are necessary to give the best chance of response to treatment.

For all these reasons the management of elderly patients represents a considerable challenge. It should be stressed that, although the guidelines for management of AML consider patients older than 60-65 years as a separate group, it is important to consider the individual patient's fitness; doctors sometimes refer to this as the biological age of the patient. For example, a very fit, healthy 70 year old may have a younger biological age than a 55 year old who has had a heart attack or who has kidney disease. Current recommendations distinguish between, on the one hand patients who are fit enough to receive intensive treatment and on the other hand those who are either not fit enough for, or do not wish to receive intensive treatment.

It remains uncertain what is the best option for patients who are either not considered fit enough for, or do not wish to receive, intensive chemotherapy. The recommendation is that, if these patients are not to be entered into a trial, they should be offered treatment with low dose cytarabine for symptom control and to improve quality of life. Although it is not curative, treatment with low-dose cytarabine does prolong survival compared with other options.

It is important to stress that palliative care is not synonymous with terminal care. Palliative care teams may be involved at an early stage to offer support to patients and family members.

Patients in this group are likely to need regular red cell and platelet transfusions along with good mouth care. Patients may receive antibiotic and antifungal treatment to reduce the risk of infection.

Patients for whom intensive treatment is appropriate would include those under 70 years of age, who have good general fitness (performance status), a white count below $100 \times 10^9/l$, no bad risk cytogenetics and no evidence of MDR (multi-drug resistance). For these patients standard induction chemotherapy with daunorubicin (or a similar drug) plus cytarabine is recommended. Some specific guidelines for this group of patients are that:

- All patients who are eligible for a study (clinical trial) should be asked to consider this option. The clinician will select which study is appropriate for the patient and provide detailed information
- There is no evidence at present to support the use of any treatment to try to overcome resistance to anti-cancer drugs
- There is insufficient evidence to support routine use of growth factors, which are compounds that stimulate the recovery of bone marrow function. Use of growth factors may be appropriate in individual cases, for example to reduce the length of hospital stay or the need for antibiotics
- The ideal post-remission therapy for older patients with AML remains unclear. There does not seem to be any benefit from extended consolidation chemotherapy or from maintenance treatment
- A new drug called gemtuzumab ozogamicin (Mylotarg™) has given promising results in treatment of patients who have relapsed and may be better tolerated than a repeat of intensive chemotherapy for these patients

Long-term effects of treatment

Long-term survival has improved dramatically, however this is most marked for younger, fitter patients and much improvement is still needed for older patients. Although efforts continue to improve survival still further, current clinical studies are also seeking to reduce the incidence and severity of adverse effects of treatments. The long-term effects of chemotherapy depend on the drugs used, the intensity of treatment and, in the case of some drugs, on the total amount of the drug received. Although there are known long-term adverse effects of certain drugs, it is more difficult to establish which drugs are responsible for which long-term effects when combinations of drugs are administered in high doses over several blocks of treatment. Individual responses to drugs vary considerably and two patients on the same treatment regimen may experience very different side effects. The specialist will discuss these aspects before treatment begins.

One common concern of patients is the effect on fertility. Alkylating agents, nitrosureas and cyclophosphamide may all adversely affect the reproductive system. These drugs may affect sperm production in males causing sterility, although most patients in recent clinical studies have regained normal sperm function on completing their chemotherapy. It is very important that patients are aware that fertility may be restored after very long periods of no sperm production. For this reason it would be unwise for a sexually active male who is apparently sterile as a consequence of chemotherapy to assume that this will always continue to be the case. In females, chemotherapy without radiotherapy is less likely to lead to sterility.

Permanent infertility is most likely in patients who have received a stem cell transplant following high doses of chemotherapy and/or whole body irradiation. An important consideration for both males and females is whether

there is a risk of adverse effects on offspring from the treatment received. A number of large studies in Britain and abroad have confirmed that there is no increased risk of cancer or of an abnormality in children whose parents received treatment for cancer. There are certain long-term consequences seen only in patients who have received stem cell transplants.⁸

Use of cranial and spinal irradiation to reduce the risk of CNS relapse is very uncommon in AML. Where whole body irradiation has been given, as part of the preparation for a stem cell transplant, it is virtually inevitable that the patient will be made sterile. Spinal or total body irradiation may also expose the thyroid gland to a dose sufficient to impair its function. For this reason, patients who have received radiotherapy that may affect the thyroid must have regular tests and may require thyroid supplements. Several years later cataracts may develop which can usually be successfully removed.

Secondary cancers are a well established, although thankfully uncommon, consequence of drug and radiation therapy for adult leukaemia. At 20 years after completion of treatment, the number of affected patients is likely to be no more than two percent. Modern treatment regimens scrupulously minimise the use of drugs and radiotherapy known to cause secondary tumours which means that the incidence will probably be significantly lower for patients being treated on current protocols.

⁸There is a separate booklet available from Leukaemia Research which discusses Stem Cell and Bone Marrow Transplantation.

Follow-up

The main purpose of follow-up of patients treated for AML is the detection of relapse and of treatment complications. During the first year following completion of chemotherapy patients are normally checked every one to two months. Checks will then gradually become less frequent until they are given annually at five years and beyond. Long-term follow-up is particularly important for those patients who have received treatments that may affect the function of the thyroid or the heart.

Prognosis

The overall prognosis for adults with AML depends both on individual patient-specific factors (e.g. age, general fitness) and on features of the disease (e.g. good or bad risk cytogenetics, whether the AML is primary or secondary). Most patients can expect to achieve a good first remission. Patients in the good risk group who are treated with chemotherapy alone have about a 70% chance of long term survival. For patients in this group who do relapse, a stem cell transplant in second remission may be feasible.

Patients in the standard- and poor-risk groups are more likely to relapse and therefore more likely to be considered for a stem cell transplant. In this case the availability of a matched sibling donor is of key significance. Patients who receive a transplant from a sibling donor have about a 50% chance of long-term survival. Survival is better in standard-risk than poor-risk patients. The outlook for patients who relapse is poor at present; if they have not already received a transplant and have a sibling donor available a transplant at this stage may be an option.



Summary

Adult acute myeloid leukaemia is a form of cancer that affects blood-producing cells in the bone marrow. Although adult AML is a very serious disease that is almost uniformly fatal if not treated, it is potentially curable with standard chemotherapy, with or without stem cell transplantation.

Treatment is based on the use of drugs in various combinations. The treatment of adult AML is based around a series of short blocks of treatment given over about four to six months, most or all of which is spent as an inpatient.

Patients in the best risk group have about a 70% chance of being long-term survivors with chemotherapy alone. For those who relapse a stem cell transplant may be an option.

Younger patients in the standard- and poor-risk groups have a somewhat better chance of survival if they have a matched sibling who can act as a donor for a stem cell transplant. The outlook for patients whose disease has relapsed tends to be poor.

Stem cell transplantation is not appropriate for all groups of patients with adult AML. It is usually recommended in first remission for selected patients in standard- and high-risk groups but not for patients in good-risk groups. Good-risk patients have a high chance of successful re-treatment after relapse so the risk of an early stem cell transplantation is not justified.

In conclusion, the prognosis for adult AML 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.

Appendix A

For many years the major system of classifying AML was based on the appearance of the leukaemic cells under the microscope. This system is described as the FAB classification after the group of French, American and British haematologists who designed it. The FAB system defines eight types of AML called M0 to M7.

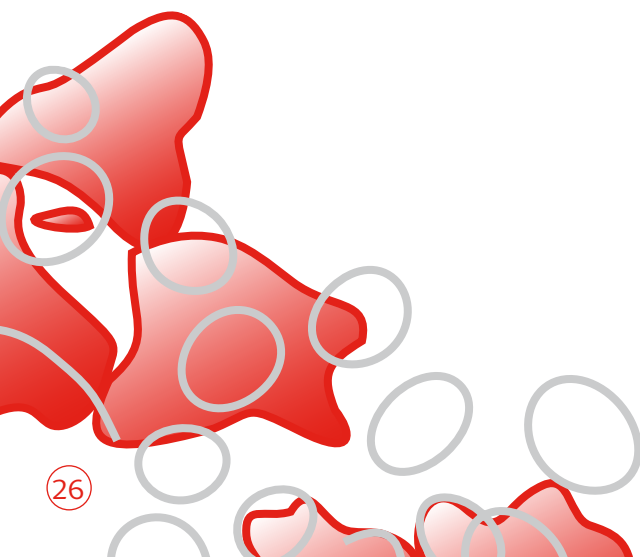
The FAB system is still important but the UK Guidelines on management of adult AML have recommended use of a newer system devised by the World Health Organization (WHO classification); this uses the FAB system but combines this with the results of other investigations to give a more detailed classification.

This still has reference to the appearance of the leukaemia cells but also considers both cytogenetics and whether or not AML has occurred after another bone marrow disorder or treatment for cancer. Because it is often necessary to start treatment before all laboratory results are available, it is common to issue a preliminary report based on the FAB system and then review treatment on the basis of the definitive WHO classification.

Immunophenotyping results are of considerable importance in the WHO classification. There may be particular difficulty in differentiating some cases of AML defined in the FAB system as M0, M1 and M7 from acute lymphoblastic leukaemia (ALL). It is very important to differentiate AML M0 from ALL because the treatment for these two diseases is very different. Both M0 and M7 are distinguished from other forms chiefly on the basis of immunophenotyping. About 50-60% of patients with AML are classified as M1, M2, M3, M6 or M7; about 40% have M4 or M5 subtypes.

The treatment is essentially the same for all except for APL which is described in a separate booklet obtainable from Leukaemia Research.

Detailed examination of chromosomes from leukaemic cells shows distinctive abnormalities in almost all cases. The study of these changes is termed cytogenetics and is of particular importance to the WHO classification. The commonest type of change is called a translocation and involves exchange of genetic material between two chromosomes. Secondary and treatment related AML are treated as separate categories in the new classification.



❖ WHO classification of AML

1. ❖ AML with recurrent translocations
 - AML with t(8;21)(q22;q22)
 - AML with t(15;17)(q22;q21) (M3, M3V)
 - AML with inv(16)(p13q22) or t(16;16)(p13;q22) (M4Eo)
 - AML with t(v;11q23)
2. ❖ AML with multilineage dysplasia
 - AML with prior myelodysplastic syndrome
 - AML without prior myelodysplastic syndrome
3. ❖ AML therapy related
 - Alkylating agent-related
 - Epipodophyllotoxin-related
4. ❖ Other
 - AML not otherwise categorised (FAB equivalent in parentheses)
 - AML minimally differentiated (M0)
 - AML without maturation (M1)
 - AML with maturation (M2)
 - Acute myelomonocytic leukaemia (M4)
 - Acute monocytic leukaemia (M5)
 - Acute erythroid leukaemia (M6)
 - Acute megakaryocytic leukaemia (M7)
 - Acute basophilic leukaemia
 - Acute panmyelosis with myelofibrosis
 - Myeloid sarcoma

❖ FAB classification of AML

The FAB classification system for AML recognises eight sub-types called M0 to M7. It is important to stress that these categories do not reflect severity of the disease, for example M0 is neither better nor worse in outlook than M7.

FAB type	Name	Special feature	% of cases
M0-M2	AML showing progressively greater maturation of leukaemic cells	Special tests may be needed to distinguish M0 from ALL	50
M3	Acute promyelocytic leukaemia	Treated with retinoic acid; haemorrhage risk	10
M4	Acute myelomonocytic leukaemia	May present with gum swelling	35-40
M5	Acute monoblastic leukaemia	As for M4	Inc. with M4
M6	Acute erythroleukaemia	Red cells affected	4
M7	Acute megakaryotic leukaemia	Platelet precursors affected	1-3

Appendix B

Risk stratification

This is based on the cytogenetic abnormalities in the leukaemia cells, and on the response to initial treatment.

Good risk:

- Any patient with favourable genetic abnormalities – t(8;21), inv(16), t(15;17) irrespective of other genetic abnormalities or response to first course of treatment

Standard:

- Any patient not in the good or poor risk groups

Poor risk:

- Any patient who still has more than 15% blasts (leukaemia cells) in the marrow after the first course of treatment, or with adverse genetic abnormalities: -5, -7, del(5q), abn (3q) or complex (5 or more) abnormalities – and without favourable genetic abnormalities.

Recent studies have shown that patients with an abnormality of a gene called FLT3 tend to have a higher risk of relapse regardless of their cytogenetic risk group.

Appendix C

CNS treatment

A potential, but uncommon, problem in the treatment of AML is central nervous system (CNS) relapse. CNS relapse appears to be a particular risk for AML M4 and M5 subtypes. The cerebro-spinal fluid (CSF), which surrounds the brain and spinal cord, contains a small number of lymphocytes in healthy people. Unfortunately, although leukaemic cells can enter the CSF, administration of drugs by mouth or by injection into a vein does not lead to sufficient accumulation in the fluid. There is therefore a risk that leukaemia cells may survive in this site. This is rare in AML, but if the doctor thinks that the patient shows symptoms or signs suggesting CNS disease, then a sample of the fluid will be obtained by a procedure called a lumbar puncture. If leukaemia cells are present then drugs will subsequently be given by the same route. All hospitals will have procedures in place to ensure that only appropriate drugs are given into the spinal fluid.

CNS involvement leading to a general relapse is far less common in AML than in ALL. This may be because the standard intravenous therapy for AML is more intensive, leading to higher drug levels in the CSF.

Appendix D

❖ Remission induction

- All patients who are eligible for a trial should be asked to consider this option. The clinician will select which trial is appropriate for the patient and provide detailed information.
- Patients who are unwilling to enter a trial, or for whom there is no trial available, should receive standard daunorubicin and cytarabine induction chemotherapy. There are two different forms of such treatment, known as 3+10 and 3+7; the specialist will recommend which option is best for a given patient.
- Patients who choose to receive non-intensive chemotherapy (and do not enter a trial) should be treated with low dose cytarabine.
- Patients who are not well enough to receive chemotherapy should receive best supportive care; usually this will mean transfusion support and possibly low doses of a drug called hydroxyurea (hydroxycarbamide) to control the white cell count. Hydroxyurea has fewer and less severe side effects than other drugs, especially when used in low doses.

❖ Consolidation treatment

- Patients who have achieved a remission and who have good risk disease or who are unwilling to consider a stem cell transplant should receive intensive chemotherapy as consolidation. A transplant remains possible as an option for these patients if they should have a relapse.
- Patients with high risk AML (as defined in Appendix Two), who achieve a remission and who have a well-matched donor may be offered a donor (allogeneic) transplant; it is accepted, however, that only a minority of patients will benefit from this.

- Standard risk patients in remission are only likely to be offered a donor transplant as part of a clinical trial.
- Allogeneic (donor) transplantation may be the treatment of choice for younger patients who are in second remission; in other words patients who have relapsed but then achieved a second remission with further treatment.
- Older patients with high risk disease or who have relapsed following a remission may be offered a reduced intensity transplant, if there is a clinical trial available which includes this as an option.
- Younger high risk patients or those who have had one or more relapses may be considered for a haplo-identical transplant, but only within a clinical trial. (A haplo-identical transplant is one from a relative who is 'half-matched' to the patient, not fully matched.)
- The role of autografting (transplants which use a patient's own stored stem cells) in the management of AML is contentious. Autografting is not routinely recommended and should only be done in the context of a clinical trial.

❖ **Treatment of relapse**

- If patients are thought unlikely to respond well to further treatment doctors may advise that palliative care is more appropriate than intensive treatment.
- If patients achieve a second remission then, depending on their age and their general health, they may be considered for a stem cell transplant.
- Most re-treatment regimens are based around use of cytarabine, almost always in combination with another drug(s).

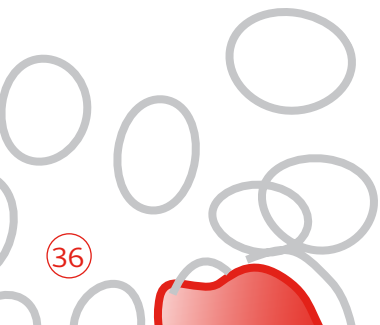
❖ **Treatment of patients over 60 years**

- All patients who are eligible for a trial should be asked to consider this option. The clinician will select which trial is appropriate for the patient and provide detailed information.
- There is no evidence at present to support the use of any treatment to try to overcome resistance to anti-cancer drugs.
- There is insufficient evidence to support routine use of growth factors, which are compounds that stimulate recovery of bone marrow function. Use of growth factors may be appropriate in individual cases, for example to reduce the length of hospital stay or the need for antibiotics.
- The ideal post-remission therapy for older patients with AML remains unclear. There does not seem to be any benefit from extended consolidation chemotherapy or from maintenance treatment.
- A new drug called gemtuzumab ozogamicin (Mylotarg™) has given promising results in treatment of patients who have relapsed and may be preferable to repeat intensive chemotherapy for patients in this situation.

Notes

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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.



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