

= Acute myeloid leukemia =

Acute myeloid leukemia ( AML ) , also known as acute myelogenous leukemia or acute nonlymphocytic leukemia ( ANLL ) , is a cancer of the myeloid line of blood cells , characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells . AML is the most common acute leukemia affecting adults , and its incidence increases with age . Although AML is a relatively rare disease , accounting for roughly 1 @. @ 2 % of cancer deaths in the United States , its incidence is expected to increase as the population ages .

The symptoms of AML are caused by replacement of normal bone marrow with leukemic cells , which causes a drop in red blood cells , platelets , and normal white blood cells . These symptoms include fatigue , shortness of breath , easy bruising and bleeding , and increased risk of infection . Several risk factors and chromosomal abnormalities have been identified , but the specific cause is not clear . As an acute leukemia , AML progresses rapidly and is typically fatal within weeks or months if left untreated .

AML has several subtypes ; treatment and prognosis vary among subtypes . AML is cured in 35 ? 40 % of people less than 60 years old and 5 ? 15 % more than 60 years old . Older people who are not able to withstand intensive chemotherapy have an average survival of 5 ? 10 months .

AML is treated initially with chemotherapy aimed at inducing a remission ; people may go on to receive additional chemotherapy or a hematopoietic stem cell transplant . Recent research into the genetics of AML has resulted in the availability of tests that can predict which drug or drugs may work best for a particular person , as well as how long that person is likely to survive . The treatment and prognosis of AML differ from those of chronic myelogenous leukemia ( CML ) in part because the cellular differentiation is not the same ; AML involves higher percentages of dedifferentiated and undifferentiated cells , including more blasts ( myeloblasts , monoblasts , and megakaryoblasts ) .

= = Signs and symptoms = =

Most signs and symptoms of AML are caused by the replacement of normal blood cells with leukemic cells . A lack of normal white blood cell production makes people more susceptible to infections ; while the leukemic cells themselves are derived from white blood cell precursors , they have no infection @-@ fighting capacity . A drop in red blood cell count ( anemia ) can cause fatigue , paleness , and shortness of breath . A lack of platelets can lead to easy bruising or bleeding with minor trauma .

The early signs of AML are often vague and nonspecific , and may be similar to those of influenza or other common illnesses . Some generalized symptoms include fever , fatigue , weight loss or loss of appetite , shortness of breath , anemia , easy bruising or bleeding , petechiae ( flat , pin @-@ head sized spots under the skin caused by bleeding ) , bone and joint pain , and persistent or frequent infections .

Enlargement of the spleen may occur in AML , but it is typically mild and asymptomatic . Lymph node swelling is rare in AML , in contrast to acute lymphoblastic leukemia . The skin is involved about 10 % of the time in the form of leukemia cutis . Rarely , Sweet 's syndrome , a paraneoplastic inflammation of the skin , can occur with AML .

Some people with AML may experience swelling of the gums because of infiltration of leukemic cells into the gum tissue . Rarely , the first sign of leukemia may be the development of a solid leukemic mass or tumor outside of the bone marrow , called a chloroma . Occasionally , a person may show no symptoms , and the leukemia may be discovered incidentally during a routine blood test .

= = Risk factors = =

A number of risk factors for developing AML have been identified , including : other blood disorders , chemical exposures , ionizing radiation , and genetics .

== Preleukemia ==

" Preleukemic " blood disorders , such as myelodysplastic syndrome ( MDS ) or myeloproliferative disease ( MPS ) , can evolve into AML ; the exact risk depends on the type of MDS / MPS .

== Chemical exposure ==

Exposure to anticancer chemotherapy , in particular alkylating agents , can increase the risk of subsequently developing AML . The risk is highest about three to five years after chemotherapy . Other chemotherapy agents , specifically epipodophyllotoxins and anthracyclines , have also been associated with treatment @-@ related leukemias , which are often associated with specific chromosomal abnormalities in the leukemic cells .

Occupational chemical exposure to benzene and other aromatic organic solvents is controversial as a cause of AML . Benzene and many of its derivatives are known to be carcinogenic in vitro . While some studies have suggested a link between occupational exposure to benzene and increased risk of AML , others have suggested the attributable risk , if any , is slight .

== Radiation ==

High amounts of ionizing radiation exposure can increase the risk of AML . Survivors of the atomic bombings of Hiroshima and Nagasaki had an increased rate of AML , as did radiologists exposed to high levels of X @-@ rays prior to the adoption of modern radiation safety practices . People treated with ionizing radiation after treatment for prostate cancer , non @-@ Hodgkin lymphoma , lung cancer and breast cancer have the highest chance of acquiring AML , but this increased risk returns to the background risk observed in the general population after 12 years .

== Genetics ==

A hereditary risk for AML appears to exist . Multiple cases of AML developing in a family at a rate higher than predicted by chance alone have been reported . Several congenital conditions may increase the risk of leukemia ; the most common is probably Down syndrome , which is associated with a 10- to 18 @-@ fold increase in the risk of AML .

== Diagnosis ==

The first clue to a diagnosis of AML is typically an abnormal result on a complete blood count . While an excess of abnormal white blood cells ( leukocytosis ) is a common finding , and leukemic blasts are sometimes seen , AML can also present with isolated decreases in platelets , red blood cells , or even with a low white blood cell count ( leukopenia ) . While a presumptive diagnosis of AML can be made by examination of the peripheral blood smear when there are circulating leukemic blasts , a definitive diagnosis usually requires an adequate bone marrow aspiration and biopsy .

Marrow or blood is examined under light microscopy , as well as flow cytometry , to diagnose the presence of leukemia , to differentiate AML from other types of leukemia ( e.g. acute lymphoblastic leukemia - ALL ) , and to classify the subtype of disease . A sample of marrow or blood is typically also tested for chromosomal abnormalities by routine cytogenetics or fluorescent in situ hybridization . Genetic studies may also be performed to look for specific mutations in genes such as FLT3 , nucleophosmin , and KIT , which may influence the outcome of the disease .

Cytochemical stains on blood and bone marrow smears are helpful in the distinction of AML from ALL , and in subclassification of AML . The combination of a myeloperoxidase or Sudan black stain and a nonspecific esterase stain will provide the desired information in most cases . The myeloperoxidase or Sudan black reactions are most useful in establishing the identity of AML and distinguishing it from ALL . The nonspecific esterase stain is used to identify a monocytic component

in AMLs and to distinguish a poorly differentiated monoblastic leukemia from ALL .

The diagnosis and classification of AML can be challenging , and should be performed by a qualified hematopathologist or hematologist . In straightforward cases , the presence of certain morphologic features ( such as Auer rods ) or specific flow cytometry results can distinguish AML from other leukemias ; however , in the absence of such features , diagnosis may be more difficult .

The two most commonly used classification schemata for AML are the older French @-@ American @-@ British ( FAB ) system and the newer World Health Organization ( WHO ) system . According to the widely used WHO criteria , the diagnosis of AML is established by demonstrating involvement of more than 20 % of the blood and / or bone marrow by leukemic myeloblasts , except in the three best prognosis forms of AML with recurrent genetic abnormalities ( t ( 8 ; 21 ) , inv ( 16 ) , and t ( 15 ; 17 ) ) in which the presence of the genetic abnormality is diagnostic irrespective of blast percent . The French ? American ? British ( FAB ) classification is a bit more stringent , requiring a blast percentage of at least 30 % in bone marrow ( BM ) or peripheral blood ( PB ) for the diagnosis of AML . AML must be carefully differentiated from " preleukemic " conditions such as myelodysplastic or myeloproliferative syndromes , which are treated differently .

Because acute promyelocytic leukemia ( APL ) has the highest curability and requires a unique form of treatment , it is important to quickly establish or exclude the diagnosis of this subtype of leukemia . Fluorescent in situ hybridization performed on blood or bone marrow is often used for this purpose , as it readily identifies the chromosomal translocation [ t ( 15 ; 17 ) ( q22 ; q12 ) ; ] that characterizes APL . There is also a need to molecularly detect the presence of PML / RARA fusion protein , which is an oncogenic product of that translocation .

= = = World Health Organization = = =

The WHO 2008 classification of acute myeloid leukemia attempts to be more clinically useful and to produce more meaningful prognostic information than the FAB criteria . Each of the WHO categories contains numerous descriptive subcategories of interest to the hematopathologist and oncologist ; however , most of the clinically significant information in the WHO schema is communicated via categorization into one of the subtypes listed below .

The WHO subtypes of AML are :

Acute leukemias of ambiguous lineage ( also known as mixed phenotype or biphenotypic acute leukemia ) occur when the leukemic cells can not be classified as either myeloid or lymphoid cells , or where both types of cells are present .

= = = French @-@ American @-@ British = = =

The French @-@ American @-@ British ( FAB ) classification system divides AML into eight subtypes , M0 through to M7 , based on the type of cell from which the leukemia developed and its degree of maturity . This is done by examining the appearance of the malignant cells with light microscopy and / or by using cytogenetics to characterize any underlying chromosomal abnormalities . The subtypes have varying prognoses and responses to therapy . Although the WHO classification ( see above ) may be more useful , the FAB system is still widely used .

Eight FAB subtypes were proposed in 1976 .

The morphologic subtypes of AML also include rare types not included in the FAB system , such as acute basophilic leukemia , which was proposed as a ninth subtype , M8 , in 1999 .

= = Pathophysiology = =

The malignant cell in AML is the myeloblast . In normal hematopoiesis , the myeloblast is an immature precursor of myeloid white blood cells ; a normal myeloblast will gradually mature into a mature white blood cell . In AML , though , a single myeloblast accumulates genetic changes which " freeze " the cell in its immature state and prevent differentiation . Such a mutation alone does not cause leukemia ; however , when such a " differentiation arrest " is combined with other mutations

which disrupt genes controlling proliferation , the result is the uncontrolled growth of an immature clone of cells , leading to the clinical entity of AML .

Much of the diversity and heterogeneity of AML stems is because leukemic transformation can occur at a number of different steps along the differentiation pathway . Modern classification schemes for AML recognize the characteristics and behavior of the leukemic cell ( and the leukemia ) may depend on the stage at which differentiation was halted .

Specific cytogenetic abnormalities can be found in many people with AML ; the types of chromosomal abnormalities often have prognostic significance . The chromosomal translocations encode abnormal fusion proteins , usually transcription factors whose altered properties may cause the " differentiation arrest " . For example , in acute promyelocytic leukemia , the t ( 15 ; 17 ) translocation produces a PML @-@ RAR? fusion protein which binds to the retinoic acid receptor element in the promoters of several myeloid @-@ specific genes and inhibits myeloid differentiation .

The clinical signs and symptoms of AML result from the growth of leukemic clone cells , which tends to displace or interfere with the development of normal blood cells in the bone marrow . This leads to neutropenia , anemia , and thrombocytopenia . The symptoms of AML are , in turn , often due to the low numbers of these normal blood elements . In rare cases , people with AML can develop a chloroma , or solid tumor of leukemic cells outside the bone marrow , which can cause various symptoms depending on its location .

An important pathophysiological mechanism of leukemogenesis in AML is the epigenetic induction of dedifferentiation by genetic mutations that alter the function of epigenetic enzymes , such as the DNA demethylase TET2 and the metabolic enzymes IDH1 and IDH2 , which lead to the generation of a novel oncometabolite , D @-@ 2 @-@ hydroxyglutarate , which inhibits the activity of epigenetic enzymes such as TET2 . The hypothesis is that such epigenetic mutations lead to the silencing of tumor suppressor genes and / or the activation of proto @-@ oncogenes .

= = Treatment = =

First @-@ line treatment of AML consists primarily of chemotherapy , and is divided into two phases : induction and postremission ( or consolidation ) therapy . The goal of induction therapy is to achieve a complete remission by reducing the number of leukemic cells to an undetectable level ; the goal of consolidation therapy is to eliminate any residual undetectable disease and achieve a cure . Hematopoietic stem cell transplantation is usually considered if induction chemotherapy fails or after a person relapses , although transplantation is also sometimes used as front @-@ line therapy for people with high @-@ risk disease . Efforts to use tyrosine kinase inhibitors in AML continue .

= = = Induction = = =

All FAB subtypes except M3 are usually given induction chemotherapy with cytarabine ( ara @-@ C ) and an anthracycline ( most often daunorubicin ) . This induction chemotherapy regimen is known as " 7 + 3 " ( or " 3 + 7 " ) , because the cytarabine is given as a continuous IV infusion for seven consecutive days while the anthracycline is given for three consecutive days as an IV push . Up to 70 % of people with AML will achieve a remission with this protocol . Other alternative induction regimens , including high @-@ dose cytarabine alone , FLAG @-@ like regimens or investigational agents , may also be used . Because of the toxic effects of therapy , including myelosuppression and an increased risk of infection , induction chemotherapy may not be offered to the very elderly , and the options may include less intense chemotherapy or palliative care .

The M3 subtype of AML , also known as acute promyelocytic leukemia ( APL ) , is almost universally treated with the drug all @-@ trans @-@ retinoic acid ( ATRA ) in addition to induction chemotherapy , usually an anthracycline . Care must be taken to prevent disseminated intravascular coagulation ( DIC ) , complicating the treatment of APL when the promyelocytes release the contents of their granules into the peripheral circulation . APL is eminently curable , with well @-@

documented treatment protocols .

The goal of the induction phase is to reach a complete remission . Complete remission does not mean the disease has been cured ; rather , it signifies no disease can be detected with available diagnostic methods . Complete remission is obtained in about 50 % ? 75 % of newly diagnosed adults , although this may vary based on the prognostic factors described above . The length of remission depends on the prognostic features of the original leukemia . In general , all remissions will fail without additional consolidation therapy .

= = = Consolidation = = =

Even after complete remission is achieved , leukemic cells likely remain in numbers too small to be detected with current diagnostic techniques . If no further postremission or consolidation therapy is given , almost all people with AML will eventually relapse . Therefore , more therapy is necessary to eliminate nondetectable disease and prevent relapse ? that is , to achieve a cure .

The specific type of postremission therapy is individualized based on a person 's prognostic factors ( see above ) and general health . For good @-@ prognosis leukemias ( i.e. inv ( 16 ) , t ( 8 ; 21 ) , and t ( 15 ; 17 ) ) , people will typically undergo an additional three to five courses of intensive chemotherapy , known as consolidation chemotherapy . For people at high risk of relapse ( e.g. those with high @-@ risk cytogenetics , underlying MDS , or therapy @-@ related AML ) , allogeneic stem cell transplantation is usually recommended if the person is able to tolerate a transplant and has a suitable donor . The best postremission therapy for intermediate @-@ risk AML ( normal cytogenetics or cytogenetic changes not falling into good @-@ risk or high @-@ risk groups ) is less clear and depends on the specific situation , including the age and overall health of the person , the person 's values , and whether a suitable stem cell donor is available .

For people who are not eligible for a stem cell transplant , immunotherapy with a combination of histamine dihydrochloride ( Ceplene ) and interleukin 2 ( Proleukin ) after the completion of consolidation has been shown to reduce the absolute relapse risk by 14 % , translating to a 50 % increase in the likelihood of maintained remission .

= = = Relapsed AML = = =

For people with relapsed AML , the only proven potentially curative therapy is a hematopoietic stem cell transplant , if one has not already been performed . In 2000 , the monoclonal antibody @-@ linked cytotoxic agent gemtuzumab ozogamicin ( Mylotarg ) was approved in the United States for people aged more than 60 years with relapsed AML who are not candidates for high @-@ dose chemotherapy . This drug was voluntarily withdrawn from the market by its manufacturer , Pfizer in 2010 .

Since treatment options for relapsed AML are so limited , palliative care or enrolment in a clinical trial may be offered .

For relapsed acute promyelocytic leukemia ( APL ) , arsenic trioxide is approved by the US FDA . Like ATRA , arsenic trioxide does not work with other subtypes of AML .

= = Prognosis = =

Acute myeloid leukemia is a curable disease ; the chance of cure for a specific person depends on a number of prognostic factors .

= = = Cytogenetics = = =

The single most important prognostic factor in AML is cytogenetics , or the chromosomal structure of the leukemic cell . Certain cytogenetic abnormalities are associated with very good outcomes ( for example , the ( 15 ; 17 ) translocation in acute promyelocytic leukemia ) . About half of people with AML have " normal " cytogenetics ; they fall into an intermediate risk group . A number of other

cytogenetic abnormalities are known to associate with a poor prognosis and a high risk of relapse after treatment .

The first publication to address cytogenetics and prognosis was the MRC trial of 1998 :

Later , the Southwest Oncology Group and Eastern Cooperative Oncology Group and , later still , Cancer and Leukemia Group B published other , mostly overlapping lists of cytogenetics prognostication in leukemia .

== Myelodysplastic syndrome ==

AML which arises from a pre-existing myelodysplastic syndrome ( MDS ) or myeloproliferative disease ( so called secondary AML ) has a worse prognosis , as does treatment-related AML arising after chemotherapy for another previous malignancy . Both of these entities are associated with a high rate of unfavorable cytogenetic abnormalities .

== Other prognostic markers ==

In some studies , age > 60 years and elevated lactate dehydrogenase level were also associated with poorer outcomes . As with most forms of cancer , performance status ( i.e. the general physical condition and activity level of the person ) plays a major role in prognosis as well .

== Genotype ==

A large number of molecular alterations are under study for their prognostic impact in AML . However , only FLT3 ITD , NPM1 , CEBPA and c-KIT are currently included in validated international risk stratification schema . These are expected to increase rapidly in the near future . FLT3 internal tandem duplications ( ITDs ) have been shown to confer a poorer prognosis in AML with normal cytogenetics . Several FLT3 inhibitors have undergone clinical trials , with mixed results . Two other mutations - NPM1 and biallelic CEBPA are associated with improved outcomes , especially in people with normal cytogenetics and are used in current risk stratification algorithms .

Researchers are investigating the clinical significance of c-KIT mutations in AML . These are prevalent , and potentially clinically relevant because of the availability of tyrosine kinase inhibitors , such as imatinib and sunitinib that can block the activity of c-KIT pharmacologically . It is expected that additional markers ( e.g. , RUNX1 , ASXL1 , and TP53 ) that have consistently been associated with an inferior outcome will soon be included in these recommendations . The prognostic importance of other mutated genes ( e.g. , DNMT3A , IDH1 , IDH2 ) is less clear .

== Expectation of cure ==

Cure rates in clinical trials have ranged from 20 ? 45 % ; although clinical trials often include only younger people and those able to tolerate aggressive therapies . The overall cure rate for all people with AML ( including the elderly and those unable to tolerate aggressive therapy ) is likely lower . Cure rates for promyelocytic leukemia can be as high as 98 % .

== Epidemiology ==

Acute myeloid leukemia is a relatively rare cancer . There are approximately 10 ,000 new cases each year in the United States , and the incidence rate has remained stable from 1995 through 2005 . AML accounts for 1 % of all cancer deaths in the United States .

The incidence of AML increases with age ; the median age at diagnosis is 63 years . AML accounts for about 90 % of all acute leukemias in adults , but is rare in children . The rate of therapy-related AML ( that is , AML caused by previous chemotherapy ) is rising ; therapy-related disease currently accounts for about 10 ? 20 % of all cases of AML . AML is slightly more common in men , with a male to female ratio of 1.3 : 1 .

There is some geographic variation in the incidence of AML . In adults , the highest rates are seen in North America , Europe , and Oceania , while adult AML is rarer in Asia and Latin America . In contrast , childhood AML is less common in North America and India than in other parts of Asia . These differences may be due to population genetics , environmental factors , or a combination of the two .

== UK ==

AML accounts for 34 % of all leukaemia cases in the UK , and around 2 @, @ 900 people were diagnosed with the disease in 2011 .

== History ==

The first published description of a case of leukemia in medical literature dates to 1827 , when French physician Alfred @-@ Armand @-@ Louis @-@ Marie Velpeau described a 63 @-@ year @-@ old florist who developed an illness characterized by fever , weakness , urinary stones , and substantial enlargement of the liver and spleen . Velpeau noted the blood of this person had a consistency " like gruel " , and speculated the appearance of the blood was due to white corpuscles . In 1845 , a series of people who died with enlarged spleens and changes in the " colors and consistencies of their blood " was reported by the Edinburgh @-@ based pathologist J.H. Bennett ; he used the term " leucocythemia " to describe this pathological condition .

The term " leukemia " was coined by Rudolf Virchow , the renowned German pathologist , in 1856 . As a pioneer in the use of the light microscope in pathology , Virchow was the first to describe the abnormal excess of white blood cells in people with the clinical syndrome described by Velpeau and Bennett . As Virchow was uncertain of the etiology of the white blood cell excess , he used the purely descriptive term " leukemia " ( Greek : " white blood " ) to refer to the condition .

Further advances in the understanding of acute myeloid leukemia occurred rapidly with the development of new technology . In 1877 , Paul Ehrlich developed a technique of staining blood films which allowed him to describe in detail normal and abnormal white blood cells . Wilhelm Ebstein introduced the term " acute leukemia " in 1889 to differentiate rapidly progressive and fatal leukemias from the more indolent chronic leukemias . The term " myeloid " was coined by Franz Ernst Christian Neumann in 1869 , as he was the first to recognize white blood cells were made in the bone marrow ( Greek : μ????? , myelos = ( bone ) marrow ) as opposed to the spleen . The technique of bone marrow examination to diagnose leukemia was first described in 1879 by Mosler . Finally , in 1900 , the myeloblast , which is the malignant cell in AML , was characterized by Otto Naegeli , who divided the leukemias into myeloid and lymphocytic .

In 2008 , AML became the first cancer genome to be fully sequenced . DNA extracted from leukemic cells were compared to unaffected skin . The leukemic cells contained acquired mutations in several genes that had not previously been associated with the disease .

== Pregnancy ==

Leukemia is rarely associated with pregnancy , affecting only about 1 in 10 @, @ 000 pregnant women . How it is handled depends primarily on the type of leukemia . Acute leukemias normally require prompt , aggressive treatment , despite significant risks of pregnancy loss and birth defects , especially if chemotherapy is given during the developmentally sensitive first trimester .