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Acute myeloid leukemia

Acute myeloid leukemia (**AML**), also known as **acute myelogenous leukemia**, 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 approximately 1.2% of cancer deaths in the United States,[1] 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. Although several risk factors for AML have been identified, the specific cause of the disease remains unclear. 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 varies among subtypes. Five-year survival varies from 15–70%, and relapse rate varies from 78–33%, depending on subtype. AML is treated initially with chemotherapy aimed at inducing a remission; patients 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 patient, as well as how long that patient is likely to survive.

Classification

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.

World Health Organization classification

The World Health Organization (WHO) 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 sub-categories 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:[2]

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 classification

The French-American-British (FAB) classification system divides AML into 8 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 under 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 below) may be more useful, the FAB system is still widely used.

There are eight FAB subtypes.[3]

Uncommon phenotypes of acute myeloid leukemia

The morphologic subtypes of AML include many exceedingly rare types not included in the FAB system. All of them except acute myeloid dendritic cell leukemia acute eosinophilic leukemia and are included in the WHO classification (see below). The following list shows these subtypes.

- Acute basophilic leukemia
- Acute eosinophilic leukemia
- Mast cell leukemia
- Acute myeloid dendritic cell leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma.

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 the patient susceptible to infections; while the leukemic cells themselves are derived from white blood cell precursors, they have no infection-fighting capacity.[4] 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 non-specific, 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.[4]

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.[4]

Some patients 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.[5]

Causes

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 or myeloproliferative disease can evolve into AML; the exact risk depends on the type of MDS/MPS.[6]

Chemical exposure

Exposure to anti-cancer chemotherapy, in particular alkylating agents, can increase the risk of subsequently developing AML. The risk is highest about 3–5 years after chemotherapy.[7] Other chemotherapy agents, specifically epipodophyllotoxins and anthracyclines, have also been associated with treatment-related leukemia. These treatment-related leukemias are often associated with specific chromosomal abnormalities in the leukemic cells.[8]

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,[9] others have suggested that the attributable risk, if any, is slight.[10]

Radiation

Ionizing radiation exposure can increase the risk of AML. Survivors of the atomic bombings of Hiroshima and Nagasaki had an increased rate of AML,[11] as did radiologists exposed to high levels of X-rays prior to the adoption of modern radiation safety practices.[12]

Genetics

A hereditary risk for AML appears to exist. There are numerous reports of multiple cases of AML developing in a family at a rate higher than predicted by chance alone.[13][14][15][16] The risk of developing AML is increased threefold in first-degree relatives of patients with AML.[17]

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.[18]

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).[19]

While a presumptive diagnosis of AML can be made via 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 via 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), and to classify the subtype of disease (see below). A sample of marrow or blood is typically also tested for chromosomal translocations 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.[20]

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 non specific 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 from ALL. The non-specific esterase stain is used to identify a monocytic component in AMLs and to distinguish a poorly differentiated monoblastic leukemia from ALL.[2]

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.[21]

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.[22] AML must be carefully differentiated from "pre-leukemic" 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]) that characterizes APL.[23]

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. However, in AML, a single myeloblast accumulates genetic changes which "freeze" the cell in its immature state and prevent differentiation.[24] 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.[25]

Much of the diversity and heterogeneity of AML stems from the fact that leukemic transformation can occur at a number of different steps along the differentiation pathway.[26] Modern classification schemes for AML recognize that 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 patients with AML; the types of chromosomal abnormalities often have prognostic significance.[27] The chromosomal translocations encode abnormal fusion proteins, usually transcription factors whose altered properties may cause the "differentiation arrest."[28] For example, in acute promyelocytic leukemia, the t(15;17) translocation produces a PML-RARα fusion protein which binds to the retinoic acid receptor element in the promoters of several myeloid-specific genes and inhibits myeloid differentiation.[29]

The clinical signs and symptoms of AML result from the fact that, as the leukemic clone of cells grows, it tends to displace or interfere with the development of normal blood cells in the bone marrow.[30] 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, patients can develop a *chloroma*, or solid tumor of leukemic cells outside the bone marrow, which can cause various symptoms depending on its location.[4]

Treatment

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 amount of leukemic cells to an undetectable level; the goal of *consolidation* therapy is to eliminate any residual undetectable disease and achieve a cure.[31]

Induction

All FAB subtypes except M3 are usually given induction chemotherapy with cytarabine (ara-C) and an anthracycline (such as daunorubicin or idarubicin).[32] 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 patients will achieve a remission with this protocol.[33] Other alternative induction regimens, including high-dose cytarabine alone or investigational agents, may also be used.[34][35] 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, is almost universally treated with the drug ATRA (all-*trans*-retinoic acid) in addition to induction chemotherapy.[36][37][38] 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 that the disease has been cured; rather, it signifies that no disease can be detected with available diagnostic methods.[32] Complete remission is obtained in about 50%–75% of newly diagnosed adults, although this may vary based on the prognostic factors described above.[39] The length of remission depends on the prognostic features of the original leukemia. In general, all remissions will fail without additional *consolidation* therapy.[40]

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 patients will eventually relapse.[41] Therefore, more therapy is necessary to eliminate non-detectable disease and prevent relapse — that is, to achieve a cure.

The specific type of postremission therapy is individualized based on a patient's prognostic factors (see above) and general health. For good-prognosis leukemias (i.e. inv(16), t(8;21), and t(15;17)), patients will typically undergo an additional 3–5 courses of intensive chemotherapy, known as *consolidation* chemotherapy.[42][43] For patients 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 patient 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 patient, the patient's personal values, and whether a suitable stem cell donor is available.[43]

For patients 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.[44]

Relapsed AML

For patients with relapsed AML, the only proven potentially curative therapy is a stem cell transplant, if one has not already been performed.[45][46][47] In 2000, the monoclonal antibody-linked cytotoxic agent gemtuzumab ozogamicin (Mylotarg) was approved in the United States for patients aged more than 60 years with relapsed AML who are not candidates for high-dose chemotherapy.[48]

Patients with relapsed AML who are not candidates for stem cell transplantion, or who have relapsed after a stem cell transplant, may be offered treatment in a clinical trial, as conventional treatment options are limited. Agents under investigation include cytotoxic drugs such as clofarabine as well as targeted therapies such as farnesyl transferase inhibitors, decitabine, and inhibitors of MDR1 (multidrug-resistance protein). Since treatment options for relapsed AML are so limited, another option which may be offered is palliative care.

For relapsed acute promyelocytic leukemia (APL), arsenic trioxide has been tested in trials and approved by the Food and Drug Administration. Like ATRA, arsenic trioxide does not work with other subtypes of AML.[49]

Prognosis

Acute myeloid leukemia is a curable disease; the chance of cure for a specific patient depends on a number of prognostic factors.[50]

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 AML patients 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.[51][52][53]

The first publication to address cytogenetics and prognosis was the MRC trial of 1998:[54]

Later, the Southwest Oncology Group and Eastern Cooperative Oncology Group,[55] and later still, Cancer and Leukemia Group B published other, mostly overlapping lists of cytogenetics prognostication in leukemia[56]

Antecedent MDS and prognosis

AML which arises from a pre-existing myelodysplastic syndrome 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.[57][58][59]

Other prognostic markers

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

FLT3 internal tandem duplications (ITDs) have been shown to confer a poorer prognosis in AML.[61] Treating these patients with more aggressive therapy, such as stem-cell transplantation in first remission, has not been shown to enhance long-term survival, so this prognostic feature is of uncertain clinical significance at this point.[62] ITDs of FLT3 may be associated with leukostasis.[63]

Researchers are investigating the clinical significance of *c-KIT* mutations in AML.[64] These are prevalent, and clinically relevant because of the availability of tyrosine kinase inhibitors, such as imatinib and sunitinib that can block the activity of *c-KIT* pharmacologically.

Other genes being investigated as prognostic factors or therapeutic targets include *CEBPA*, *BAALC*, *ERG*, and *NPM1*.

Overall expectation of cure

Cure rates in clinical trials have ranged from 20–45%;[65][66] however, it should be noted that clinical trials often include only younger patients and those able to tolerate aggressive therapies. The overall cure rate for all patients 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%.[67]

Epidemiology

Acute myeloid leukemia is a relatively rare cancer. There are approximately 10,500 new cases each year in the United States, and the incidence rate has remained stable from 1995 through 2005. AML accounts for 1.2% of all cancer deaths in the United States.[1]

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.[1] 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.[68] AML is slightly more common in men, with a male-to-female ratio of 1.3:1.[69]

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.[70][71] In contrast, childhood AML is less common in North America and India than in other parts of Asia.[72] These differences may be due to population genetics, environmental factors, or a combination of the two.

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 that the blood of this patient had a consistency "like gruel", and speculated that the appearance of the blood was due to white

corpuscles.[73] In 1845, a series of patients 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.[74]

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 patients with the clinical syndrome described by Velpeau and Bennett. As Virchow was uncertain of the cause of the white blood cell excess, he used the purely descriptive term "leukemia" (Greek: "white blood") to refer to the condition.[75]

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.[76] The term "myeloid" was coined by Neumann in 1869, as he was the first to recognize that white blood cells were made in the bone marrow (Greek: μυελός, *myelos* = (bone) marrow) as opposed to the spleen. The technique of bone marrow examination to diagnose leukemia was first described in 1879 by Mosler.[77] Finally, in 1900 the myeloblast, which is the malignant cell in AML, was characterized by Naegeli, who divided the leukemias into *myeloid* and *lymphocytic*.[78][79]

In 2008, AML became the first cancer genome to be fully sequenced. DNA extracted from leukemic cells were compared to unaffected skin.[80] The leukemic cells contained acquired mutations in several genes that had not previously been associated with the disease.

See also

- Chloroma
- Chronic myelogenous leukemia
- Acute lymphoblastic leukemia

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External links

Acute Myeloid Leukemia at American Cancer Society

Acute Myeloid Leukemia at Leukemia & Lymphoma Society

Childhood Acute Myeloid Leukemia at cchs.net

PDQ statement on AML for health professionals at National Cancer Institute