All About Acute Myeloid Leukemia (AML)

This article is a more specific discussion of AML. Please be sure to read Leukemia: The Basics first, so you have a basic understanding of leukemia.

What is AML?

Acute myelogenous leukemia, acute myelocytic leukemia, acute granulocytic leukemia and acute non-lymphocytic leukemia (AML) is a blood cancer that affects white blood cells, red blood cells, and/or platelets. A person with AML develops abnormal numbers of these cells very quickly, giving the disease the name "acute." The white blood cell (WBC) count may be higher or lower than normal, but the WBCs that are being produced do not function well. Because WBCs are an important part of fighting infections, patients often have multiple infections that don't respond to treatment before they are diagnosed. Some people will have low red blood cell or platelet counts, but this is not always the case.

What causes AML and am I at risk?

There are an estimated 21,450 cases diagnosed annually in the United States, accounting for over 30% of all leukemia cases, but only 1.2% of all new cancer cases annually. AML can occur at any age, but is more common in adults, particularly over age 55, with the average age at diagnosis being 68 years. The incidence of AML increases with age and is more common in men than in women.

Although we do not know what causes every case of AML, there are certain exposures that can increase risk. Exposure to ionizing radiation, such as from an atomic bomb or working in the nuclear industry, increases risk slightly (the increase has been seen in nuclear workers, but not people living near nuclear plants). Exposure to benzene increases the risk of developing AML. Smoking cigarettes is the most common way people are exposed to benzene, although some may be exposed to this chemical in their jobs. A history of blood or genetic disorders, such as myelodysplasia, Fanconi's Anemia, NF1, and Li Fraumeni syndrome all increase the risk of developing AML. Risk is also increased in children with Down Syndrome (trisomy 21). There is an increased risk for people with a first-degree relative (parent, sibling, child) with the disease.

Previous treatment with chemotherapy or radiation can lead to AML, which is often called treatment-related AML. This is thought to account for between 10 and 20% of AML cases. The risk is thought to be most strongly linked with certain chemotherapy agents. In the case of AML caused by alkylating agents (ifosfamide, cisplatin, melphalan, cytoxan, etc.), it typically occurs 5 to 7 years after exposure to the chemotherapy (known as a "latent period"). It tends to start as an myelodysplastic syndrome, which is a bone marrow disorder that results in abnormal blood cell counts. AML caused by treatment with alkylating agents carries a poor prognosis, as the disease is often not as responsive to treatment. Risk after radiation treatment alone, given without these chemotherapy agents, is relatively low.

A second category of treatment-related AML is those caused by a group of medications called topoisomerase II inhibitors, which include etoposide, doxorubicin, daunorubicin, and mitoxantrone. These cases generally occur less than 3 years after treatment with the agent. Unfortunately, they are also not very responsive to therapy.

How can I prevent AML?

In most AML cases, we don’t know the cause of the diagnosis. Thus, there aren’t any ways to prevent AML from developing. It is important to exercise, avoid tobacco use, and maintain a nutritious diet to lower your risk of cancer in general.

What screening tests are used for AML?
There are no standard screening tests used for AML. Be sure to tell your health care providers of any history of being exposed to radiation (as in an atomic bomb detonation or nuclear accident), exposure to benzene, if you have a history of smoking, have previously received radiation or chemotherapy or have a genetic syndrome.

**What are the signs of AML?**

In AML, certain blood cells do not fully mature and cannot function properly. These immature cells, called "blasts," also suppress normal blood cells from forming and further compound the problem. Symptoms are related to the abnormal numbers and function of blood cells. They can include fever, infection, easy bleeding or bruising, shortness of breath, loss of appetite, headaches and fatigue. These symptoms can also be signs of common illnesses like the flu. It is not uncommon for a person to be seen several times by a healthcare provider before receiving a diagnosis of AML. Most infections are just infections and not leukemia, so treating a suspected infection is appropriate and this short delay in diagnosis is not likely to affect the course of the disease. It is important that you return to your healthcare provider for further investigation if your symptoms are not improving with the prescribed treatment (often antibiotics).

AML is most often discovered when a person has an infection that does not improve with treatment or unexplained bleeding or bruising. When a blood count is checked, the counts return with abnormal results or blasts seen in the sample. Once this occurs, further testing is required to determine the type of AML.

**How is AML diagnosed?**

Once AML is suspected, further blood tests may be drawn and a bone marrow biopsy and aspiration performed to classify the type of AML. Other tests, including cytogenetic testing (karyotype and/or FISH testing), immunophenotyping, molecular testing, and human leukocyte antigen (HLA) typing for potential future bone marrow transplant will be performed. Classification helps to guide treatment plans. There are two classification systems for AML (See classification systems below).

If you are experiencing any neurologic symptoms at the time of diagnosis (headache, change in mental status, confusion, etc.), a lumbar puncture and/or CT scan or MRI (links) of the head may be performed to see if leukemia cells are present in the spinal fluid. In some cases, CT scans or x-rays may be used to evaluate leukemia involvement in other organs. All patients who will receive anthracycline chemotherapy (idarubicin or daunorubicin) will require a test to evaluate their heart function called a MUGA (Multiple Gated Acquisition) Scan prior to starting therapy to determine that their heart can tolerate the therapy and establish a baseline to compare to if future chemotherapy is needed or the chemotherapy causes any damage to the heart.

**WHO Classification of AML and Related Neoplasms**

The World Health Organization (WHO) uses genetic abnormalities to classify categories of AML. This system changed the threshold for the diagnosis of AML to >20% blast cells in the bone marrow. It groups various subtypes of AML based on genetic abnormalities and prognosis. Patients with AML may have abnormalities detected in certain genes, which gives the physician some information about prognosis. Patients can be classified into prognostic risk groups (favorable, intermediate and poor) based on the genetic abnormalities present, which may help determine the most appropriate course of therapy.

The World Health Organization classification is complex and can be difficult to understand, but it is provided here because you may hear your team discussing your leukemia using this system.

**Acute myeloid leukemia (AML) and related neoplasms.**

- AML with recurrent genetic abnormalities.
  - AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1.
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1q22);CBFB-MYH11.
  - APL with PML-RARA.
  - AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A.
    - AML with t(8;9)(p23;q34.1);DEK-NUP214.
    - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM.
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1.
Provisional entity: AML with BCR-ABL1.
- AML with mutated NPM1.
- AML with biallelic mutations of CEBPA.
- Provisional entity: AML with mutated RUNX1.
- AML with myelodysplasia-related changes.
- Therapy-related myeloid neoplasms.
  - AML, NOS.
  - AML with minimal differentiation.
  - AML without maturation.
  - AML with maturation.
  - Acute myelomonocytic leukemia.
  - Acute monoblastic/monocytic leukemia.
  - Pure erythroid leukemia.
  - Acute megakaryoblastic leukemia.
  - Acute basophilic leukemia.
  - Acute panmyelosis with myelofibrosis.
- Myeloid sarcoma.
- Myeloid proliferations related to Down syndrome.
  - Transient abnormal myelopoiesis (TAM).
  - Myeloid leukemia associated with Down syndrome.
- Blastic plasmacytoid dendritic cell neoplasm.

**Acute leukemias of ambiguous lineage.**

- Acute undifferentiated leukemia.
- Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1.
- MPAL with t(v;11q23.3); KMT2A rearranged.
- MPAL, B/myeloid, NOS.
- MPAL, T/myeloid, NOS.

**Myeloid neoplasms with germline predisposition without a preexisting disorder or organ dysfunction.**

- AML with germline CEBPA mutation.
- Myeloid neoplasms with germline DDX41 mutation.

**Myeloid neoplasms with germline predisposition and preexisting platelet disorders.**

**Myeloid neoplasms with germline predisposition and other organ dysfunction.**

**How is AML treated?**

Chemotherapy for AML is very complex. It is broken down into two phases, induction phase, and consolidation (or intensification) phase. The goal of induction therapy is to induce a remission, usually defined as less than 5% blast cells found in the bone marrow. Once remission is achieved, consolidation therapy is given. Surgery is not used because AML is a disease of the blood, which circulates throughout the whole body; this means an effective treatment must address disease throughout the body. The selection of a chemotherapy regimen is dependent on age, as well as the subtype of AML.

The treatment is designed to wipe out the abnormally functioning leukemia cells, but this treatment also destroys many healthy cells, putting the patient at risk for bleeding and infection, which can be life-threatening. In addition, chemotherapy medications can cause side effects such as mouth sores (mucositis), diarrhea, nausea/vomiting, and hair loss (alopecia).

In patients who are under 60 years old, induction chemotherapy for AML is typically a combination of two chemotherapy agents: cytarabine (given for 7 days) and daunorubicin, idarubicin, fludarabine, or cladribine (given for 3 or 5 days, depending on the medication used). The goal of this therapy is to induce a remission. If remission does not occur, induction chemotherapy
can be repeated or a new chemotherapy regimen can be given.

Once remission is achieved, chemotherapy is continued for 4-5 more cycles (4-6 months), generally with cytarabine alone, in higher doses. This is the consolidation phase.

The use of different therapies for those over the age of 60 came about because patients over 60 have been found to have poorer responses to standard therapy, regardless of their overall health. This may be a result of yet unidentified genetic abnormalities in these patients. The induction phase for patients over the age of 60 typically includes a similar combination of medications, but sometimes they are given at a lower intensity than in younger patients. Other medications used in the treatment of those over the age of 60 include venetoclax, glasdegib, gemtuzumab, enasidenib, mitoxantrone, decitabine, azacitidine, midostaurin, and clofarabine.

Some patients who cannot tolerate any therapy may be offered supportive care. Supportive care is not curative. The goal of supportive care is to maintain quality of life for the patient. This includes treatment with blood and platelet transfusions and hydroxyurea. Hydroxyurea is used to lower the white blood cell count, which can help relieve symptoms caused by a high count, such as pain.

**Acute Promyelocytic Leukemia (APL or APML)**

APML is a type of AML whose treatment has changed dramatically in the past 20 years. Previously one of the deadliest forms of AML, this subtype is now considered curable in many patients. In the 1970s and 80s, researchers discovered an abnormal protein in cells caused by the 15;17 translocation (genetic abnormality), which leads to the development of APML. This abnormal protein prevents the immature blood cells from differentiating (or progressing) into functioning, mature cells. A medication called all-trans retinoic acid (ATRA) allows these immature cells (also called blasts) to mature and die. ATRA is given in combination with an anthracycline chemotherapy (daunorubicin or idarubicin) and arsenic trioxide in the induction phase. These medications (or cytarabine or mitoxantrone) are used at different doses over a longer period of time in the consolidation phase. Gemtuzumab ozogamicin is also used in combination with ATRA and arsenic trioxide to treat APML.

APML is often associated with a condition of abnormal bleeding and blood clotting called DIC (disseminated intravascular coagulation). In DIC, the body is making blood clots where it should not and rapidly uses up the components necessary for blood clotting. This leads to bleeding at the same time as these clots are being formed. Patients with this complication will require various blood product transfusions and emergent treatment of the leukemia. The condition is a result of the leukemia, so it must be treated in order for the DIC to resolve.

**Measurable/Minimal Residual Disease (MRD) Testing**

Measurable or minimal residual disease (MRD) testing is used to see if the cancer treatment is working and to guide further treatment plans. MRD tests use highly sensitive methods, including multi-parametric flow cytometry and polymerase chain reaction (PCR). These methods look for any remaining cancer cells that cannot be seen in routine tests. This test can detect even 1 cancer cell among 1 million normal cells. Currently, MRD testing is being studied extensively so treatment teams can better understand how to use it in planning treatment after induction as well as if outcomes differ as a result of knowing more about MRD.

**Bone Marrow Transplant**

Post consolidation treatment may include an allogeneic bone marrow transplant from a matched sibling or unrelated donor. The decision to pursue bone marrow transplantation is based on the subtype of AML, as well as genetic abnormalities associated with the patient’s AML, the age of the patient (generally under age 60), and their health. The goal of bone marrow transplant is to achieve a cure or improve long term survival. Clinical trials are currently underway to study bone marrow transplants in patients over 60 years of age with favorable genetics and few health problems.

**Complications & Concerns of Leukemia and Treatment**

**Leukocytosis**

Some people with AML will present with a very high white blood cell count, which is called leukocytosis. This can cause symptoms, including headache, shortness of breath and pain. In some cases, chemotherapy will be started right away to lower the white blood cell count, but in other cases, it may take a few days to clarify the diagnosis or complete the pretreatment testing.
(bone marrow biopsy, heart function testing). For those patients, leukopheresis may be performed while the testing is completed. This is a procedure that removes white blood cells from the blood and returns the rest of the blood to the patient (it is similar to dialysis). Another option is to administer a medication called hydroxyurea that lowers the white blood cell count also, although there is some controversy as to which method is more effective. Either is a temporary reduction in the WBC count, which without further chemotherapy, will continue to rise.

**Other Treatment Complications**

People with leukemia are at risk of infection (due to few and poorly functioning white blood cells) and bleeding (due to low numbers of platelets) even before any therapy is started. Because these abnormalities are a result of the leukemia, it is necessary to treat the leukemia in order to correct the abnormal blood counts. Leukemia treatment causes the blood cell counts and function to temporarily get worse. During this time, patients will receive blood and platelet transfusions, antibiotics, and take precautions to prevent infection and bleeding.

Hand washing is the single best way to prevent infection and should be performed frequently by patients, visitors, caregivers, and healthcare personnel. Even the best hand washers get infections, so we implement a few other restrictions to help in the cause. People with leukemia may have restrictions on consuming some types of fresh fruit and vegetables or receiving fresh flowers or plants while in the hospital. (See the gift guide for ideas on what to send a patient with these restrictions) You may think this sounds odd, but these items can harbor bacteria and may put the patient at higher risk of infection. We ask people who are sick (or who have sick family members at home) not visit the patient in person and if they absolutely must, they need to wear a mask and wash their hands well.

In most cases, some type of infection or fever is inevitable. When this happens, the patient will typically have several tests done to look for a source of the infection, which can include blood, urine and stool cultures, and a chest x-ray. Antibiotics may be started, or adjusted if they are already being given. Many times, the source of the infection is never identified and general antibiotics that treat a variety of things will be used. The patient will receive these antibiotics until their white blood count reaches a level that will allow them to fight the infection on their own.

Over the course of their treatment, patients with AML will require either blood (for low hemoglobin levels) or platelet (for low platelet counts) transfusions. People with low hemoglobin counts (also called anemia) can experience fatigue, shortness of breath or appear pale. A low platelet count (also called thrombocytopenia) can lead to bleeding. This can be as small as gums bleeding when brushing the teeth or a nosebleed to dangerous bleeding, such as a stroke. Patients should use caution to avoid bumping themselves with normal activities; they may not shave with a razor (an electric razor is okay, with caution) and should avoid any activities that increase the risk of bleeding or bruising. Patients should always inform their healthcare team if they have symptoms of anemia or thrombocytopenia.

**Clinical Trials**

There are clinical research trials for most types of cancer, and every stage of the disease. Clinical trials are designed to determine the value of specific treatments. Trials are often designed to treat a certain stage of cancer, either as the first form of treatment offered or as an option for treatment after other treatments have failed to work. They can be used to evaluate medications or treatments to prevent cancer, detect it earlier, or help manage side effects. Clinical trials are extremely important in furthering our knowledge of the disease. It is through clinical trials that we know what we do today, and many exciting new therapies are currently being tested. Talk to your provider about participating in clinical trials in your area. You can also explore currently open clinical trials using the OncoLink Clinical Trials Matching Service.

**Follow Up Care and Survivorship**

After completion of consolidation chemotherapy, guidelines suggest patients have routine lab work to monitor for relapse. These labs include a complete blood count (CBC) with platelets every 1-3 months for 2 years, then every 3-6 months for years 3-5 after treatment. Repeat bone marrow biopsy and aspirate may be performed if the lab work reveals any abnormalities.

Fear of relapse, relationship challenges, the financial impact of cancer treatment, employment issues, and coping strategies are common emotional and practical issues experienced by AML survivors. Your healthcare team can identify resources for support and management of these practical and emotional challenges faced during and after cancer.
Cancer survivorship is a relatively new focus of oncology care. With some 17 million cancer survivors in the US alone, there is a need to help patients transition from active treatment to survivorship. What happens next, how do you get back to normal, what should you know and do to live healthy going forward? A survivorship care plan can be a first step in educating yourself about navigating life after cancer and helping you communicate knowledgeably with your healthcare providers. Create a survivorship care plan today on OncoLink.

Resources for More Information

Leukemia and Lymphoma Society
Provides disease information and support resources.

http://www.lls.org/

Leukemia Research Foundation
Provides disease information and a glossary of medical terms related to leukemia.

http://www.leukemia-research.org

American Society of Hematology
The official website of doctors who treat blood disorders including leukemia.

http://www.hematology.org/Patients/Cancers/Leukemia.aspx

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