ACUTE MYELOID LEUKEMIA (AML)

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What is Acute myeloid leukemia (AML)?

Blood cells are formed in the bone marrow. Blood precursor cells from the bone marrow can either become a myeloid cell or a lymphoid cell. A myeloid cell can form the following 3 types of blood cells: 1. Red blood cells which carry oxygen and other substances to the all body parts. 2. Platelets which form blood clots to stop bleeding in case of injury. 3. White blood cells which help us fight infection and disease. A lymphoid cell can form the following 3 types of blood cells: 1. B cells which make antibodies (a type of protein) to help fight infection. 2. T cells which directly fight new and repeat infections and also help the B-lymphocytes to make antibodies. 3. Natural killer cells which attack cancer cells and viruses.

Leukemia is a cancer which grows from the white blood cells. Normally white blood cells help us fight infections. In leukemia, the cancerous cells crowd out the normal cells in the blood and bone marrow. Hence the normal white blood cells are not able to work properly.

If the leukemia progresses rapidly, it is called acute leukemia while the leukemias which progress slowly are called chronic leukemias. In acute myeloid leukemia or AML, abnormal immature myeloid cells called myeloid blasts accumulate in the marrow and blood. Because of this, the marrow is not able to produce normal healthy blood cells.

Who is affected by AML?

Studies from India show that the median age of hospitalized patients with AML is around 40 years which is at least 2 decades earlier than what is seen in developed countries (Kapoor R et al. ASH 2018). AML is more common in males. The incidence of AML increases with advancing age.

What causes AML?

Doctors do not really know what causes leukemia. You cannot catch leukemia from someone else and you cannot give it to anyone else. It usually cannot be passed on from parent to child (except rare forms of familial acute myeloid leukemias). The uncontrolled multiplication of myeloid cells in the marrow and lack of development of these cells into mature cells is thought to be linked to genetic abnormalities. These genetic abnormalities can be either large changes called chromosomal abnormalities seen in about 50-60% patients or small changes called mutated genes. Many of these changes can occur together. Risk factors to develop AML are as follows:

1. Patients who have undergone chemotherapy in the past for another cancer
2. Patients who have an underlying bone marrow disease like bone marrow failure or myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN)
3. People exposed to benzene, which is a component of crude oil and gasoline, household glues, cleaning products, tobacco smoke, paint stripping products and pesticides.
• **What are the symptoms of AML?**

Symptom is a change which a patient sees or feels. In AML, due to shortage of healthy blood cells, patients can have the following symptoms:

1. Symptoms related to anemia or reduced red cell blood cells - Fatigue, weakness, shortness of breath during normal activities, dizziness, headaches
2. Symptoms related reduced normal white blood cells – fever, frequent infections
3. Symptoms related to reduced platelets – easy bruisability, red spots on the skin (called petechiae), nose bleeding, gum bleeding
4. Other symptoms of AML – swollen gums, loss of appetite, weight loss, bone or joint pain, fullness in abdomen due to enlarged liver or spleen, lumps over skin or any other part of the body (due to accumulation of AML cells outside the marrow – this condition is called a “myeloid sarcoma”)

• **What tests are done for AML?**

In patients with AML, other than history and physical examination, the following tests are usually done:

- Complete blood counts with peripheral smear examination
- Metabolic panel including electrolytes, kidney and liver function tests, calcium, phosphate, uric acid, lactate dehydrogenase
- Blood clotting tests: PT, aPTT and fibrinogen
- Virology screen: HIV, HbsAg and anti-HCV
- Bone marrow examination – aspiration, biopsy, cytochemistry, immunophenotyping, cytogenetics and molecular tests (see the lab module for details – also see the bone marrow procedure video)
- CT brain if bleeding in the brain is suspected or MRI brain and lumbar puncture if disease involvement in the brain is suspected
- PET/CT if myeloid sarcomas or involvement of AML cells in areas other than the marrow is suspected
- Test for heart function like ECG and echocardiography before starting chemotherapy
- HLA typing for the patient and siblings and/or unrelated donor search in case a transplant is necessary
• **How is the diagnosis of AML confirmed?**

Generally, the identification of 20 percent or more leukemia cells of myeloid origin in the peripheral blood and/or bone marrow sample is required to confirm an AML diagnosis. This is usually supported by bone marrow cytochemistry and immunophenotyping tests. Less often, a diagnosis of AML is made in patients with less than 20 percent blasts based on cytogenetic tests. In patients with myeloid sarcoma, AML cells in areas other than bone marrow can be confirmed using biopsy and special tests on the biopsy like immunohistochemistry.

• **What are subtypes of AML?**

Cytogenetic and molecular analyses help to classify patients with AML as having a low, intermediate or high chance of relapse (re-occurrence of the disease) which will impact on their choice of treatments.

There are 3 risk groups in AML:

- Most Favorable
- Intermediate
- Least favorable

**Most Favorable risk** category includes the following:

- Translocation between chromosomes 8 and 21: t(8;21);
- Inversion of chromosome 16: inv(16);
- Translocation within chromosome 16 itself: t(16:16);
- Translocation between chromosomes 15 and 17: t(15;17) (also called acute promyelocytic leukemia or APL);
- Mutations in both copies of *CEBPA*;
- Mutation in *NPM1* without *FLT3-ITD* mutation

**Intermediate risk** category includes the following:

- Mutation in *NPM1* and *FLT3-ITD*\(^{high}\)
- No mutation in *NPM1* and *FLT3-ITD* or with *FLT3-ITD*\(^{low}\) in absence of adverse risk genetic lesions
- Translocation between chromosome 9 and 11: t(9;11)
- Chromosomal abnormalities not classified as favorable or adverse

**Least favorable risk** category includes the following:

- Complex changes involving 3 or more chromosomal abnormalities;
• Monosomal karyotype (having a single copy of a chromosome pair instead of the usual two copies, plus at least one additional monosomy or structural chromosomal abnormality);
• Deletion of part of chromosome 5 or 7: 5q- or 7q-; or monosomy of chromosomes 5 or 7: -5 or -7
• Deletion of part of chromosome 17: 17p-; or monosomy of chromosome 17 with an abnormality of 17p: -17/abn(17p)
• Abnormalities of chromosome 11 (at the region q23): 11q23
• Translocation or inversion of chromosome 3: inv(3) or t(3:3);
• Translocation between chromosomes 6 and 9: t(6;9);
• Translocation between chromosomes 9 and 22: t(9;22);
• FLT3-ITD\textsuperscript{high} without NPM1 mutation
• Mutation in RUNX1 or ASXL1 or TP53

• What are the treatment options for AML?

• **Acute promyelocytic leukemia (APL) is treated differently from other AML subtypes**

  Patients with APL are generally subdivided into the following two groups according to their white blood count as treatment recommendations can differ for each group: 1. Low- to intermediate-risk: patients with a white blood cell count of 10,000 cells per microlitre of blood or less. 2. High-risk: patients with a white blood cell count of more than 10,000 cells per microlitre of blood.

  Medications used to treat APL include the following:

  1. **All trans retinoic acid (ATRA)** is an oral medication given twice daily which forces the APL blasts to mature and become normal cells. ATRA can cause differentiation syndrome wherein there is release of large amounts of immune substances from the leukemia cells. This causes fever, leg swelling, breathing difficulty and weight gain. It is usually treated with steroids like dexamethasone and sometimes require temporary stopping of ATRA.

  2. **Arsenic trioxide (ATO)** is a medication which is given intravenously over 1-2 hours once daily. It is similar to ATRA in its mode of action; however it also causes death of the APL blasts. Combination of ATRA and ATO results in long term cure of APL in most patients with low-intermediate risk APL. ATO can cause serious irregular heart rhythms (arrhythmias). Hence monitoring of electrocardiogram (ECG), serum potassium and magnesium is done while on ATO therapy and sometimes the medications are stopped if the ECG shows abnormalities. ATO also can cause differentiation syndrome similar to that caused with ATRA.
3. **Anthracyclines** like idarubicin or mitoxantrone, which act by interacting directly with the DNA of the leukemic cells and interfering with their survival, are used in combination with ATRA and ATO for treating patients with high risk APL. These are given over 2-3 days as intravenous injections once daily during the initial treatment. These medications can be given if the heart function is normal. Also, the use of these medications can rarely cause other cancers much later in life.

4. **Other medications** include hydroxyurea (antimetabolite which acts as a substitute for the DNA or RNA building blocks of the leukemic cells) which is given to reduce the white cell counts during initial treatment.

Phases of treatment in APL are:

**Induction:** During induction phase, for low-intermediate risk APL, the treatment consists of combination of daily injections of ATO along with the oral medication ATRA given twice daily. For patients with high risk APL, anthracycline chemotherapy is also given for 2 to 3 days as once daily injections. Hydroxyurea capsules are given orally till the white cell count is high in the first few days. Based on the blood clotting tests, blood, platelet and plasma transfusions are given for the first 2-3 weeks to reduce the risk of bleeding complications.

After 6-8 weeks of treatment, bone marrow tests are repeated to look for disease control. Most patients will have good disease control (complete remission) after 6-8 weeks of treatment.

**Consolidation:** During the consolidation phase which usually starts after 4 weeks of completing the induction phase treatment, the same medications used in induction are used in different schedules. A bone marrow test is repeated after consolidation to see if there is disease control at a much deeper level (molecular remission using PCR test).

**Maintenance:** Some treatment protocols include maintenance therapy for 1-2 years after completing consolidation therapy.

The total treatment cost is approximately Rs 6 to 7 lacs (Bankar et al. BJH 2020)

**Acute myeloid leukemia (AML)**

The current standard treatment for AML consists of induction chemotherapy with a combination of cytarabine and an anthracycline, followed by consolidation therapy with chemotherapy or a stem cell transplant. Chemotherapy kill fast growing cells throughout the body – both cancer cells and healthy cells. Different chemotherapy medications work in different ways against the leukemia cells. Hence a combination of different chemotherapy medications is used for treatment. Each treatment cycle is made up of a certain number of days of treatment followed by rest for the healthy cells to recover before starting the next cycle.
The goal of induction chemotherapy is to achieve “complete remission” i.e. less than 5% blast cells in the bone marrow after the patient’s healthy blood cells have returned to normal levels after chemotherapy.

For adult patients, usually a chemotherapy called “7+3” which consists of 3 days of a medication called daunorubicin and 7 continuous days of a medication called cytosine is used. Before giving daunorubicin, in some patients, testing of the heart function (example – echocardiography) is done especially if they are above 35-40 years of age. These chemotherapy medications are given via a long venous catheter (central line). The catheter helps to give medicines into the veins for a prolonged period of time. It also helps to collect blood sample without having to use needle pricks.

During and after the chemotherapy, there can be side effects like fever, bleeding, skin rash and others (see chemotherapy section). Blood and platelet transfusions and medications to reduce the risk of fungal infections are given during this period. In case of fever, antibiotics are also given. Despite all the supportive care, there is approximately a 20% risk to life during the first induction chemotherapy (Kapoor R et al. ASH 2018).

Usually a bone marrow test is done after 1 week of the chemotherapy to see if the leukemia cells have reduced in the bone marrow. This test is again repeated at 4-6 weeks again after the cell counts in the blood comes back to normal to see if there is control of the leukemia (complete remission).

Depending upon the results of this bone marrow test and results of the cytogenetic and molecular tests, a decision is made to either give more courses of chemotherapy or to do stem cell transplantation.

If bone marrow test results show good control of the leukemia and cytogenetic and molecular test results show favorable risk disease, then further chemotherapy cycles alone are advised. During these chemotherapy cycles, the chemotherapy medication cytosine is given usually twice a day over 3 alternate days. Before starting this medication, eye drops are given to reduce the risk of conjunctivitis with this medication. Also, physical examination to test balance and coordination is done before each dose of this medication.

If the bone marrow test results show good control of the leukemia and cytogenetic and molecular test results show intermediate risk disease, then the decision of giving chemotherapy or transplant is taken depending upon the availability of a matched stem cell donor (chosen on the basis of HLA test).

If the bone marrow test results show good control of the leukemia and cytogenetic and molecular test results show less favorable risk disease, then stem cell transplant is advised. For this, a stem cell donor has to be identified. This is done on the basis of HLA test. Usually siblings have 25% chance of being HLA matched. If siblings are not matched, then a search is performed in unrelated voluntary stem cell donor registries to find a HLA matched donor. If no match exists,
then stem cell transplant using donors who are not fully matched is planned after discussion of the risks and benefits.

The cost of induction chemotherapy is approximately Rs. 7 to 8 lacs. The cost of consolidation chemotherapy is approximately Rs 3 to 4 lacs. The cost of stem cell transplantation varies according to the donor; it is approximately Rs 15-20 lacs for a matched sibling donor transplantation. (Philip C et al. BJH 2015)

For pediatric patients, the treatment consists similarly of induction chemotherapy with slightly different combination of medications followed by 4-5 courses of consolidation chemotherapy +/- maintenance therapy. Some patients are offered stem cell transplantation based on the results of the bone marrow done after induction chemotherapy and results of the cytogenetic and molecular tests.

Older patients (above 60 years of age) with AML or those having additional diseases other than AML (like heart disease, kidney disease, lung disease, etc) or those patients who are very sick when AML is detected have higher risks during treatment with intensive chemotherapies like 7+3. These patients are offered treatment with medications called hypomethylating agents. Azacytidine which is given as an injection for 7 days in a month or decitabine which is given as an injection for 5 days in a month. These medications take a few months to show response.

Few new medications have been approved for use in AML recently. They are:

1. Gemtuzumab ozogamicin – This is a type of targeted therapy that is linked to a chemotherapy medication. It attaches to a cell surface protein called CD33 which is present in the leukemia cells in many patients with AML. Then it enters the cell and the chemotherapy medication is released. This medication is used in patients with favorable risk AML and some patients with intermediate risk AML. Its potential side effect is liver injury.

2. FLT3 inhibitors – Midostaurin is an oral medication which is given twice daily along with the induction chemotherapy and each cycle of consolidation therapy in patients with AML who have FLT3 mutation detected on molecular tests.

3. Venetoclax – This is another oral medication which is generally used along with azacitidine, decitabine or low dose cytosine for treatment of patients with AML who are unable to tolerate intensive chemotherapy.

4. IDH inhibitors –ivosidenib and enasidenib – these oral medications used in patients with AML who have IDH mutations detected on molecular tests. These medications are used in patients who are unable to tolerate intensive chemotherapy or in patients in whom the disease has recurred after initial treatment.
• **What tests are done to check response to treatment? What is the chance of cure/control?**

Usually, bone marrow tests are done to check response to treatment. (see bone marrow aspirate, biopsy and immunophenotyping from the Lab module)).

The chance of cure for the disease depends on factors like age, other illness, response to the chemotherapy, cytogenetic and molecular test results.

Generally acute promyelocytic leukemia has an excellent chance of cure, especially in low-intermediate category. The risk to life is mainly in the first few weeks of therapy wherein there is increased risk due to bleeding complications. Children with AML also have a good chance of cure. In adults in general, AML is usually associated with a long-term chance of cure of approximately 30-40% however this varies depending upon the results of other tests. Whereas in older patients with AML, the long-term chance of cure is lower.

• **What if there is no response to initial treatment or if the disease comes back after treatment?**

**Acute promyelocytic leukemia**

The chance of having no response to initial treatment is extremely low when using the current standard treatment. When the disease come back after initial treatment, induction therapy with arsenic trioxide, all-trans retinoic acid and chemotherapy is restarted. After induction, consolidation course with these medications is given. After consolidation, if the disease is controlled at a molecular level (molecular remission using PCR test), then autologous transplantation is offered. In an autologous transplantation, stem cells are taken from the patient and stored in a frozen state. After giving high dose chemotherapy, these cells are given back to the patient so that they can form normal bone marrow cells again.

If disease is detected at molecular level using PCR test, then allogeneic stem cell transplantation is offered. This need a HLA matched donor.

**Acute myeloid leukemia**

If there is no response to initial treatment, then another chemotherapy course with different medications is started. Once the disease is controlled, a stem cell transplant is offered.

If the disease comes back after initial treatment, then chemotherapy is started again. Once the disease is controlled, a stem cell transplant is offered.

The usual chemotherapy medications used are amongst the following: fludarabine, cytosine, idarubicin, mitoxantrone, etoposide, daunorubicin.

The chances of cure depends upon factors like time interval between completion of initial treatment and diagnosis of the recurrence of disease, the cytogenetic test results and the age.
In patients who are not fit for intensive chemotherapy, targeted therapies like FLT3 inhibitors (gilteritinib) and IDH inhibitors (ivosidenib or enasidenib) are offered. If the disease keeps coming back again or does not respond to treatment, then the chance of achieving cure is low. In such a scenario, one option is to choose palliative treatment. This therapy makes use of treatments like low dose cytosine, hypomethylating agents and supportive care like blood and platelet transfusions. The goal of palliative therapy is to attain good quality of life for the maximum possible time without trying to cure the disease.

- **What is the total duration of the treatment? How frequent are the hospital visits after completing treatment and how long is follow up required? Any late effects of treatment?**

For APL, the treatment duration is usually 1 year. On follow up, some patients who are at high risk for disease recurrence (intermediate-high risk) are monitored every 3 months with PCR test for approximately 2 years.

For children with AML who do not require transplant as consolidation, the treatment duration is approximately 6 months of intensive treatment (induction + consolidation) followed by maintenance therapy for a year.

For adults with AML who do not require transplant as consolidation, the treatment duration is approximately 5 months (induction for 1 month followed by 3 cycles of consolidation every month).

For patients requiring transplantation as consolidation, the treatment duration is approximately 1-2 months for initial intensive treatment (induction) and another 1-2 months for the transplant (as consolidation) followed by 3-6 months of frequent hospital visits.

Once the disease is controlled and the consolidation therapy (either chemotherapy or transplant) is completed, the follow up is usually every 2-3 months for 2 years and then every 3-6 months for upto 5 years. Complete blood counts are done on follow up visits. Bone marrow is not required unless the blood counts show any abnormality.

Late effect of treatment that can happen include sterility, heart disease, memory or concentration changes, disease of endocrine glands and bone disease.

- **What is a clinical trial? Are there any clinical trials on this disease in India?**

Every new treatment or practice is studied methodically in series of studies called “clinical trials” before it becomes a part of standard treatment. Clinical trials are carefully designed and continuously monitored by expert clinicians and researchers to ensure patient safety and scientific accuracy. Patient participation in past clinical trials has resulted in the “standard” treatments and practices which we have today. Ongoing clinical trials on AML in India can be found at [http://ctri.nic.in/Clinicaltrials/login.php](http://ctri.nic.in/Clinicaltrials/login.php)