LEUKEMIA & LYMPHOMA SOCIETY®

Acute Promyelocytic Leukemia Facts

No. 26 in a series providing the latest information for patients, caregivers and healthcare professionals

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Highlights

- Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia (AML) in which cells in the bone marrow that produce blood cells (red cells, white cells and platelets) do not develop and function normally.
- APL begins with one or more acquired changes (mutations) to the DNA of a single blood-forming cell. APL cells have a very specific abnormality that involves chromosomes 15 and 17, leading to the formation of an abnormal fusion gene *PML/RARa*. This mutated gene causes many of the features of the disease.
- In APL, promyelocytes (immature white cells) are overproduced and accumulate in the bone marrow. Signs, symptoms and complications of APL result from the overproduction of promyelocytes and the underproduction of healthy blood cells.
- Treatment with a drug called ATRA (all-*trans* retinoic acid) that targets the chromosomal abnormality, has proven very successful. Probably even more than ATRA, arsenic trioxide (ATO) is also effective as a single agent in APL. Other drug therapies that have increased remission and cure rates include anthracyclines and gemtuzumab ozogamicin (GO).
- Because of advances in diagnosis and treatment of this disease, APL is now considered the most curable form of adult leukemia. Cure rates of 90 percent have been reported from centers specializing in APL treatment.
- A common symptom of APL is bleeding. This is due to reduced numbers of platelets and deficiencies in clotting factors. Bleeding can be life threatening and is managed by treating the APL and by employing supportive measures such as the transfusion of platelets and blood clotting factors. Medical supervision of individuals with APL is important to prevent or treat any disease or treatment complications.

Introduction

Leukemia is a cancer of the marrow and blood. The four major types of leukemia are acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). Each of the main types of leukemia is further classified into subtypes.

With myeloid leukemia, a cancerous change begins in a marrow cell that normally forms certain blood cells—that is, red cells, some types of white cells and platelets. Most people diagnosed with AML have one of the eight subtypes shown in the following table.

Table 1. AML Subtypes Based on the FAB Classification

FAB Subtype	Name
M0	AML minimally differentiated
M1	AML with minimal maturation
M2	AML with maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M4 eos	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryoblastic leukemia

Table 1. AML subtypes based on the French-American-British (FAB) classification. AML cells may have features of red cells, platelets or white cells (monocytes, eosinophils or, rarely, basophils or mast cells) in addition to myeloblasts or promyelocytes. AML subtypes M0 through M5 start in early white cells, subtype M6 starts in early red cells while subtype M7 starts in early platelet cells.

Acute promyelocytic leukemia (APL) is a unique subtype of acute myeloid leukemia. APL is classified as the M3 subtype of AML according to the French-American-British (FAB) system and as APL with translocation between chromosomes 15 and 17 [t(15;17)] in the World Health Organization (WHO) classification system. It accounts for about 10 to 15 percent of all adult AML cases diagnosed in the United States each year.

With APL, promyelocytes (immature white cells) accumulate in the marrow. These cells stop maturing during the step in blood cell formation that comes after the development

Support for this publication provided by TEVA

of myeloblasts. They also have a specific chromosome abnormality that involves a translocation of chromosome 15 and chromosome 17 (t15;17).

Treatment for APL differs from all other AML treatments. Because of advances in diagnosis and treatment, APL has been transformed from the most fatal to the most curable form of acute leukemia in adults.

This fact sheet provides current information about diagnosis, treatment, new treatments being investigated in clinical trials and support resources.

Causes and Incidence

Most APL cells have a specific chromosome abnormality involving a balanced translocation (swapping) between chromosomes 15 and 17 (t15;17), resulting in the abnormal fusion gene *PML/RARα*. This abnormality is not only a distinguishing feature of APL that causes the symptoms of the disease, but also a key target of treatment.

According to data from the National Cancer Institute SEER registry (from 1992 to 2007), the age-adjusted annual incidence (newly diagnosed cases) of APL was 0.23 per 100,000 persons. During that period, the average age of APL diagnosis was 44 years, which is younger than that of patients with other types of AML.

The incidence of APL is equal among males and females. Some reports indicate a higher incidence in Hispanics and a lower incidence for African Americans. APL patients are more often obese than other patients with AML. The disease is most commonly diagnosed in patients ranging from 20 to 50 years of age.

With current treatment, APL has become one of the most curable types of acute leukemia. People with APL who receive treatment often have a normal or near-normal quality of life.

Signs and Symptoms

It is common for people with APL to feel a loss of well-being because of the underproduction of normal blood cells and accumulation of leukemic cells in the bone marrow.

Common signs and symptoms of APL include

- A pale complexion from anemia
- Signs of bleeding caused by a very low platelet count, including
  - Black-and-blue marks or bruises occurring for no reason or because of a minor injury
  - The appearance of pinhead-sized red spots on the skin, called "petechiae"
  - Prolonged bleeding from minor cuts.
- Fatigue
- Mild fever
- Swollen gums
- Frequent minor infections
- Loss of appetite
- Weight loss
- Discomfort in bones or joints
- Enlarged spleen
- Enlarged liver
- Neurological symptoms (headache, confusion, visual changes)—associated with APL that involves the central nervous system.

Bleeding. A low platelet count and low amounts of clotting factors predispose patients to bleeding. Bleeding in the brain or lung is serious and can be fatal. However, such bleeding is usually preceded by minor bleeding, such as nosebleeds, blood in the urine or bruises.

Infection. Severe infection may be present at the time of diagnosis but it becomes more common and often more serious during treatment, when the bone marrow is completely suppressed.

Diagnosis

When a patient is suspected of having leukemia, obtaining an accurate diagnosis of the type of leukemia is important. The exact diagnosis helps the doctor to estimate how the disease will progress and determine the appropriate course of treatment. Some of the tests used for making a diagnosis may also be repeated during and after therapy to measure the effects of treatment.

Blood and Bone Marrow Tests. A change in the number and appearance of blood cells helps the doctor to make an accurate diagnosis. APL cells may look similar to normal immature white cells. However, their development is incomplete.

Blood samples are generally taken from a vein in the patient's arm. Samples of marrow cells are obtained by bone marrow aspiration and biopsy. The cells from the blood and marrow samples are examined under a microscope.

Other Tests. "Karyotyping" and "fluorescence in situ hybridization (FISH)" are tests used to identify certain changes in chromosomes and genes. A laboratory test called a "polymerase chain reaction (PCR)" may be done in which cells in a sample of blood or marrow are studied to look for certain changes in the structure or function of genes.

APL cells have a very specific abnormality called a "balanced translocation," in which parts of the chromosomes 15 and 17 are swapped over. This results in the formation of an abnormal fusion gene known as "*PML/RARa*." This mutated gene causes many of the features of the disease. A diagnosis of APL requires demonstration of the 15;17 translocation or of the *PML/RARa* gene.

In APL, promyelocytes (immature white cells) are overproduced and accumulate in the bone marrow. Promyelocytes are unable to mature, leading to a significant reduction of white cells and also preventing the development of other normal blood cells. Signs, symptoms and complications of APL result from the overproduction of promyelocytes and the underproduction of healthy blood cells.

Doctors use the results of the blood and bone marrow tests to identify the abnormal APL cells. A prompt diagnosis of APL is vital because appropriate treatment must be started immediately in order to avoid the serious and potentially life-threatening complications associated with the disease.

When this type of leukemia is suspected, doctors may order "coagulation status" tests along with other laboratory tests and imaging scans, to help rule out the presence of blood clots. Some conditions that these tests help prevent or diagnose include deep-vein thrombosis, pulmonary embolism and strokes.

For more information about bone marrow tests and other lab tests, please see the free LLS booklet *Understanding Lab and Imaging Tests* at www.LLS.org/booklets.

Treatment Planning

Treatment decisions are based on the patient's age, general health and APL risk classification.

APL is classified into the two following categories of risk based on the patient's white blood cell count at the moment of diagnosis:

- Low risk—white blood cell (WBC) count 10,000/microliter (µL) or less
- High risk—WBC count greater than 10,000/µL.

Typically, patients with low-risk disease are treated with less intensive regimens than those used for patients at high risk. Nonetheless, every patient's medical situation is different and should be evaluated individually by a hematologist/oncologist, a doctor who specializes in treating blood cancers. It is important for you and members of your medical team to discuss all treatment options, including treatments being studied in clinical trials.

For more information about choosing a doctor or a treatment center, see the free LLS publication *Choosing a Blood Cancer Specialist or Treatment Center* at www.LLS.org/booklets.

Treatment

Treatment goals for the disease are

- To control symptoms
- To decrease the risk of complications.

Therapies are aimed at

- Targeting the (t15;17) that causes the abnormal fusion gene *PML/RARa*, characteristic of APL cells
- Bringing blood cell counts to normal or near-normal levels
- Decreasing APL-related symptoms.

Drug Therapy

Bleeding into the brain or lungs is a potentially fatal complication of APL. For this reason, treatment should be initiated once the diagnosis is suspected after examination of the blood and bone marrow tests, even if the presence of the translocation 15;17 or the *PML/RARa* gene has not been confirmed.

All-*trans* retinoic acid (ATRA)— This drug, a vitamin A derivative, has become a standard component of induction therapy for APL. ATRA is also known as "tretinoin (Vesanoid®)." ATRA is capable of eliminating the *PML/RARa* abnormality, thus inducing the leukemic promyelocytes to develop into mature cells (neutrophils). It causes a marked decrease in the concentration of leukemic blast cells in the marrow, and a remission frequently follows.

Used alone, ATRA can induce a short-term remission in at least 80 percent of patients. Treatment with ATRA must be followed by or given with arsenic trioxide and/or chemotherapy in order for the remission to be long lasting. ATRA often minimizes the side effects of chemotherapy because blood cell counts may be improved and the number of leukemic cells may be decreased at the time that chemotherapy is started.

Anthracyclines—These chemotherapy agents interact directly with the DNA in the nucleus of leukemic cells, interfering with cell survival. There are several types of anthracyclines but daunorubicin (Cerubidine®) and idarubicin (Idamycin®) are the ones most commonly used in the treatment of APL, typically in combination with ATRA. The remission rate of APL patients treated with ATRA and an anthracycline, such as idarubicin, is about 70 to 80 percent.

Antimetabolites—These chemotherapy agents substitute for the DNA or RNA building blocks within a leukemic cell, preventing the cell from growing. For people with high-risk APL (white cell count greater than 10,000/µL at diagnosis), the antimetabolite cytarabine may be added to induction or consolidation regimens.

Arsenic Trioxide (ATO)—Until recently, the standard of care in APL treatment involved combining ATRA with anthracycline-based chemotherapy during both the induction and consolidation phases of treatment. Recently, randomized studies from Italy and the United Kingdom have shown that in patients with low-risk APL the combination of ATO and ATRA is superior to the former standard of ATRA and anthracyclines. The possibility of receiving optimal treatment with ATO and ATRA without the addition of chemotherapy drugs may be beneficial to children and older patients who may be particularly susceptible to the toxic effects of excessive anthracycline exposure. Arsenic trioxide (Trisenox®), given intravenously, is FDA approved in combination with tretinoin for treatment of adults with newly-diagnosed low-risk APL whose APL is characterized by the presence of the t(15;17) translocation or *PML/RARA* gene expression.

ATO is also the recommended therapy for patients who do not achieve a molecular remission at the end of consolidation or who relapse later on in the treatment. For patients with high-risk APL, combinations of ATO, ATRA, and anthracyclines are commonly used.

APL Treatment Side Effects and Supportive Care

Management of side effects is important. If you have any concerns about your side effects, talk to your doctor to get help. Most side effects are temporary and resolve when treatment is completed. However, patients with APL may need specific kinds of supportive care.

Differentiation Syndrome. Treatment for APL is often associated with a variety of symptoms and abnormal conditions, including fluid retention, labored breathing, fluid accumulation around the heart or lungs, and episodes of low blood pressure. This group of symptoms is known as "differentiation syndrome." Patients should be closely monitored for the development of these symptoms since differentiation syndrome along with hemorrhage, are the leading causes of death during induction therapy. Early recognition and the prompt start of corticosteroid therapy are essential to manage this potential complication.

QT Interval Prolongation. The use of arsenic trioxide (ATO) can affect electrolyte levels (essential minerals in the blood such as potassium, magnesium, and calcium), which can cause a heart rhythm disorder known as "QT interval prolongation." This disorder causes fast heartbeats that may lead to sudden fainting or seizures. Electrolytes should be monitored before and during APL treatment to ensure that they stay within a normal reference range. The clinicians on your treatment team may order routine blood work and electrocardiograms to monitor any negative effects of ATO and other drugs.

Bleeding. The ability to form blood clots is impaired in APL patients because patients have a decreased number of platelets and clotting factors. This condition is also known as "coagulopathy." It is important to screen for this problem with specific blood tests as part of the initial workup of newly diagnosed patients as well as before any invasive procedure. When coagulopathy symptoms are present, patients are supported with transfusion therapy.

Childhood APL

APL in children or adolescents shares many features with APL in adults. Pediatric patients are, however, more likely to present with high-risk features including an elevated white blood cell count at diagnosis.

Typically, pediatric patients are treated with the same or very similar regimens as the ones used for adult patients. Treatment outcomes are similar in adult and pediatric patients although recent studies have indicated that very young children may be at higher risk of relapse.

The successful use of the drug combination ATRA and ATO holds great promise in the treatment of pediatric APL. The possibility of receiving optimal treatment with these two agents without the addition of chemotherapy drugs may be of particular benefit to pediatric patients who are extremely sensitive to the toxic effects of anthracycline therapy, which may cause heart and other organ damage.

For children who receive intensive chemotherapy, including anthracyclines, ongoing monitoring of cardiac function is critical. Periodic examination of kidney function and auditory exams are also recommended. Children with this disease should have their care coordinated by pediatric hematology/oncology specialists and be treated in cancer centers or hospitals with the appropriate supportive care facilities and services.

For more information, see the free LLS publications *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma* and *Learning & Living with Cancer: Advocating for your child's educational needs*.

Treatment for Patients with Relapsed or Refractory APL

Despite high remission rates after induction therapy, resistance to treatment and relapse occur in a number of patients, just as they do in some patients with other types of AML. Therefore, long-term follow-up care of patients in remission is required to identify those who are cured and those who may require further therapy.

Arsenic trioxide (Trisenox®), given intravenously, is FDA approved for induction of remission and consolidation in patients with APL who are refractory to, or have relapsed

from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or *PML/RARA* gene expression.

Central Nervous System (CNS) APL. A small number of patients with APL develop disease in their cerebrospinal fluid, the watery fluid that bathes the brain and the spinal cord. Symptoms of CNS APL are headaches and various neurological manifestations, such as confusion and visual changes. CNS APL is most often diagnosed in patients thought to be in remission and is associated with patients who present with a high white blood cell count at diagnosis. This type of APL is treated with spinal taps and chemotherapy into the spinal fluid, which is known as "intrathecal therapy."

Stem Cell Transplantation. A small number of APL patients have persistent minimal residual disease (MRD) at the end of consolidation therapy. These patients may benefit from arsenic trioxide (Trisenox®), followed by autologous or, if a suitable donor is available, allogeneic stem cell transplantation.

For more information about stem cell transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation* at www.LLS.org/booklets.

Treatments Undergoing Investigation

Patients are encouraged to explore, and enter if they are eligible, clinical trials. Clinical trials test new drugs and treatments, many of which are supported by LLS research programs, before they are approved by the FDA as standard treatments.

Clinical trials are carefully controlled research studies, conducted under rigorous guidelines, to help researchers determine the beneficial effects and possible adverse side effects of new treatments. Clinical trials are designed to be accurate and very safe. Patient participation in clinical trials is important in the development of new and more effective treatments for APL and may provide patients with additional treatment options.

Patients interested in participating in clinical trials are encouraged to talk to their doctors about whether a clinical trial would be appropriate for them.

For more information about clinical trials, see the free LLS publication *Understanding Clinical Trials for Blood Cancers* at www.LLS.org/booklets or visit www.LLS.org/clinicaltrials.

Current research approaches under investigation include

Gemtuzumab ozogamicin (GO)— This agent is an antibody-drug conjugate that pairs the antitumor antibiotic calicheamicin to an anti-CD33 antibody. This drug was FDA approved in 2000 based on its success treating older patients with relapsed AML but was later taken off the market when studies indicated it did not offer long-term benefits due to potential adverse side effects. It is once again under study, in combination with ATRA, as it has shown results in selected APL patients who have not responded to all other treatment options.

Differentiation therapy— This concept involves studying the use of all-*trans* retinoic acid (ATRA), which is approved to treat APL, in combination with some types of histone deacetylase inhibitor drugs such as valproic acid (VPA) to promote the growth and differentiation of immature leukemic blast cells.

Tamibarotene— This drug is a synthetic retinoid recently approved in Japan for the treatment of relapsed or refractory APL. Early studies suggest that this agent may be a more powerful inducer of APL cell differentiation than ATRA while causing milder side effects. Tamibarotene is currently being studied in the United States as a single agent and in combination with other drugs for patients with relapsed or refractory disease.

We encourage you to contact an Information Specialist (visit www.LLS.org/informationspecialists) for more information about specific treatments under study in clinical trials.

Treatment Outcomes

The likely outcome of a disease, called the "prognosis," depends on many factors. Each patient's risk factors, which affect his or her prognosis, are evaluated individually.

Because of advances in diagnostic techniques and modern treatments, APL is today considered to be the most curable subtype of acute myeloid leukemia in adults, with complete remission rates of 90 percent and cure rates of approximately 80 percent and even higher among low-risk patients. However, some studies suggest cure rates may be lower when APL is not treated in centers with experience in treating the disease.

Although highly curable with current therapies, APL is still linked with a significant incidence of early death (during the initial course of treatment) due to the characteristic bleeding complications associated with the disease. It is important for patients to be carefully monitored by their treatment professionals to prevent and treat any complications caused by the disease or its treatment.

Acknowledgement

LLS gratefully acknowledges

Elihu Estey, MD
Professor, Division of Hematology, University of Washington School of Medicine
Member, Fred Hutchinson Cancer Research Center
Seattle, WA

for his review of *Acute Promyelocytic Leukemia Facts* and his important contributions to the material presented in this publication.

We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the country and in Canada. To find the chapter nearest to you, visit our website at www.LLS.org/chapterfind or contact:

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573
Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers. The following lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team's knowledge and skills.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please:

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/booklets.

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Telephone/Web Education Programs. LLS offers free telephone/web education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients to reach out to others in similar circumstances, and share information. For more information, please visit www.LLS.org/chat or www.LLS.org/discussionboard.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, blood cancer conferences and other great resources.

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please:

- Call: (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical-trial searches
- Visit: www.LLS.org/clinicaltrials

Advocacy. LLS enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Other Resources

CANCER*Care*
www.cancercare.org
(800) 813-4673

CANCERCare provides free professional support services to anyone affected by cancer: people with cancer, caregivers, children, loved ones and the bereaved.

Cancer Support Community (CSC)
www.cancersupportcommunity.org
(888) 793-9355

CSC strives to optimize patient care by providing essential but often overlooked services including support groups, counseling, education and healthy lifestyle programs. CSC provides emotional and social support through a network of more than 50 local affiliates, 100 satellite locations and online.

The National Cancer Institute (NCI)
www.cancer.gov
(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including promyelocytic leukemia (APL). The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where APL patients can look for clinical trials.

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