Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML)

No. 17 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) are uncommon blood cancers that are classified by the World Health Organization (WHO) as "mixed myelodysplastic/myeloproliferative diseases."
- CMML and JMML each start with one or more acquired changes (mutations) to the DNA of a single cell called a "monocyte" (a type of blood cell).
- For CMML, the median age at diagnosis ranges from 65 to 75 years. Common CMML symptoms include weakness, fatigue, unexplained bruising and/or bleeding, infection and enlarged liver and/or spleen. Most CMML patients are treated with drug therapy. Allogeneic stem cell transplantation is a potential curative option for a small number of patients.
- JMML is most commonly diagnosed in infants and children younger than 6 years. Common JMML symptoms include pallor, developmental delays, decrease in appetite, irritability, enlarged abdomen, dry cough, rash, enlarged liver and/or spleen and enlarged lymph nodes. Most JMML patients are treated with drug therapy and allogeneic stem cell transplantation, a potentially curative treatment for JMML
- The safety and effectiveness of new therapies for CMML and JMML are being researched in clinical trials.

This fact sheet provides additional information about the diagnosis, treatment, clinical trials, expected outcomes and support resources for CMML and JMML.

Introduction

Chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) are uncommon blood cancers that have characteristics of two other types of blood cancers called "myelodysplastic syndromes" (MDS) and "myeloproliferative disorders" (MPDs). For this reason the World Health Organization (WHO) has classified CMML and JMML as "mixed myelodysplastic/myeloproliferative diseases." This is a relatively new (2001) classification that is expected to lead to greater understanding of these diseases and to the development of more effective treatments. CMML and JMML were previously classified as myelodysplastic syndromes (MDS) subtypes or atypical chronic myeloid disorders.

Published as a public service by The Leukemia & Lymphoma Society • 1311 Mamaroneck Avenue • White Plains, NY 10605
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Chronic Myelomonocytic Leukemia (CMML)

CMML is a clonal disorder, which means that it begins with one or more changes (mutations) to the DNA of a single cell that multiplies uncontrollably. In CMML the change affects the normal development of a type of white cell called a "monocyte."

Monocytes arise from immature blood-forming cells called "myeloblasts" and "myelocytes." In CMML, the myeloblasts and myelocytes accumulate in the marrow and in other organs, and interfere with the normal production of monocytes and other types of blood cells, including red blood cells (which carry oxygen to all the tissues of the body) and platelets (which form plugs to help stop bleeding after an injury).

Monocytes represent about 5 to 10 percent of the cells in normal human blood. These cells and other white cells called "neutrophils" are the two major microbe-eating and microbe-killing cells in the blood. When monocytes leave the blood and enter the tissue, they are converted to macrophages. The macrophage is the monocyte-in-action: it can combat infection in the tissues, ingest dead cells and assist other cells, such as lymphocytes, in carrying out their immune functions.

The WHO classification categorizes CMML into two subtypes based on the percentage of blast cells (also referred to as "blasts") found in the blood and marrow:

- CMML-1—Less than 5 percent blasts in the blood and less than 10 percent blasts in the marrow
- CMML-2—5 to 19 percent blasts in the blood and 10 to 19 percent blasts in the marrow.

In most healthy individuals, blast cells represent less than 5 percent of developing marrow cells.

CMML Incidence

CMML affects approximately 3 out of 100,000 individuals in the United States each year. The median age at diagnosis ranges from 65 to 75 years. Seventy-five percent of patients are older than 60 years at the time of diagnosis. CMML has been reported in a small number of older children and younger adults. There are approximately twice as many male CMML patients as female CMML patients.

Signs and Symptoms of CMML

Signs and symptoms may include

- Weakness and fatigue due to "anemia" (a decrease below normal in the number of red cells and, consequently, in the hemoglobin concentration of the blood)
- Petechiae (pinhead-sized sites of bleeding in the skin), bruising and bleeding due to "thrombocytopenia" (low platelet counts)
- Infections due to "leukopenia" (a below-normal concentration of white cells)
- Enlargement of the spleen and/or liver
- Feeling of fullness below the ribs due to spleen enlargement.

Diagnosis of CMML

Patients who are eventually diagnosed with CMML may seek medical attention at first because of physical weakness, infection or unexplained bleeding. A diagnosis of CMML usually cannot be confirmed with one lab test result that shows abnormal blood counts. The diagnosis can only be confirmed after a patient has been monitored for a period of time with repeat lab tests to rule out other forms of myelodysplastic syndromes (MDS) and myeloproliferative disorders (MPDs).

Generally, the tests used in the diagnosis of CMML include additional blood tests and bone marrow aspiration and biopsy to check for

- A persistent elevated monocyte count in the blood (greater than 1,000/microliter [1,000/µl] of blood)
- Less than 20 percent blasts in the blood or the marrow
- Signs of abnormalities in one or more of the types of precursor cells that develop into red cells, certain types of white cells or platelets.

Other diagnostic tests for CMML may include

- X-rays and/or computed tomography (CT) scans of the abdomen and pelvis to detect the enlargement of the spleen and liver
- Cytogenetic tests that confirm the absence of the Philadelphia (Ph) chromosome or the *BCR-ABL* gene associated with chronic myelogenous leukemia (CML)
- Blood and urine tests to detect elevated "lysozyme" levels. Lysozyme is an enzyme that functions as an antibacterial agent and is found in saliva, tears and some immune cells such as monocytes
- Blood tests to detect elevated levels of proteins such as "lactate dehydrogenase" (LDH) and "beta 2-microglobulin." LDH levels may become elevated when there is tissue damage in the body. Beta 2-microglobulin levels may increase as a result of increased production or destruction of white cells, due to inflammation or to certain types of cancer.

Genetic Mutations. Twenty to 40 percent of CMML patients have chromosomal abnormalities. About 1 to 4 percent of CMML patients have an abnormality called a "translocation" (a piece of one chromosome breaks off and attaches to another chromosome, which can lead to the development of an "oncogene" (cancer-causing gene). In CMML the translocation involves the *PDGFR*-β and *TEL* genes. Patients that have the *PDGFR*-β and *TEL* gene mutation may respond favorably to treatment with the drug imatinib (Gleevec®). See *Drug Therapy for CMML* on page 4.

Other chromosomal abnormalities associated with CMML, which may be tested for only in a research setting, include

- Monosomy 7 and trisomy 8, which are the most common chromosomal abnormalities in CMML patients.
- Mutation of a specific gene within the gene family known as *"RAS,"* such as the *K-RAS* or *N-RAS* genes. *RAS* genes and the proteins they encode regulate cell growth. When a mutation of a *RAS* gene occurs, cells multiply uncontrollably. This type of mutation occurs in about 35 percent of CMML patients.

For additional information about lab and imaging tests, please see the free LLS booklet *Understanding Lab and Imaging Tests.*

Treatment of CMML

For most CMML patients, the disease is treatable, but not curable, with currently available therapies. Patients are advised to

- Seek treatment from a physician who is experienced in treating CMML or from a physician who is in consultation with a center or physician who has experience treating this disease
- Discuss the most appropriate treatment for their situation with their physician.

The type of treatment depends on various patient factors, including the

- Nature and extent of symptoms
- Need for rapid disease control
- Eligibility for stem cell transplantation
- Overall health and quality of life.

Drug Therapy for CMML. There is no one standard treatment for CMML. Treatment for previously untreated or relapsed CMML patients may include standard-dose or low-dose cytarabine (Cytosar-U®), etoposide (VePesid®) and hydroxyurea (Hydrea®). Treatment with these agents has been useful for a small number of patients.

Azacitidine (Vidaza®) and decitabine (Dacogen®), approved for treating MDS, are also approved for treating CMML patients. However, the effectiveness of azacitidine and decitabine for CMML treatment requires further study.

The small number (about 1 to 4 percent) of CMML patients who have the *PDGFR*-β and *TEL* gene mutation (see *Genetic Mutations,* page 3) are treated with the drug imatinib (Gleevec®). This treatment usually results in a return to normal blood counts, cytogenetic remissions, and, occasionally, molecular remissions for these CMML patients. Gleevec is an oral medication that is approved to treat chronic myelogenous leukemia (CML) and some other diseases.

Stem Cell Transplantation for CMML. Allogeneic stem cell transplantation (giving the patient stem cells from either a related or unrelated matched donor) has been used to treat and sometimes cure CMML patients. However, because allogeneic stem cell transplantation is associated with a relatively high mortality risk that increases with patient age, most CMML patients are not eligible for this therapy. It is an option for a small number of patients—generally, younger patients with an advanced disease, who have either failed to respond to or are no longer responding to other treatment and who have an appropriate stem cell donor. Ongoing clinical trials for reduced-intensity allogeneic stem cell transplantation may prove effective and make this treatment option available to more patients in the future. See *Clinical Trials for CMML* below for more information.

For additional information about stem cell transplantation, please see the free LLS booklet *Blood and Marrow Stem Cell Transplantation.*

Clinical Trials for CMML

Patient participation in clinical trials is important in order to develop new and better treatments. Patients are encouraged to talk to their physicians about whether taking part in a clinical trial would be a good treatment option for them.

Examples of the types of therapies currently under study for CMML treatment are listed here.

Decitabine (Dacogen), currently approved to treat CMML, is being studied for use in combination with other agents such as vorinostat (Zolinza®) and arsenic trioxide (Trisenox®) for CMML patients who have not responded to treatment or who have relapsed after initial therapy.

Studies have indicated that the GM-CSF (granulocyte macrophage-colony stimulating factor) fusion protein DT388 GM-CSF has the ability to kill CMML cells while sparing normal cells. The fusion of GM-CSF with DT388 (a toxin) allows the targeting of cells with GM-CSF receptors, such as CMML cells.

Reduced-intensity allogeneic stem cell transplantation (also known as "nonmyeloablative allogeneic stem cell transplantation") may prove effective for CMML patients who do not respond to drug therapy but are not considered candidates for allogeneic transplant because of older age or other health risks. Patients being conditioned for a reduced-intensity transplant receive lower doses of chemotherapy and/or radiation than those given to patients before a standard stem cell transplantation. Immunosuppressive drugs are used to prevent rejection of the graft, and the engraftment of donor immune cells may allow these cells to attack the disease (graft-versus-leukemia effect). The theory being tested with a reduced-intensity transplant is that by undergoing less-toxic conditioning prior to the transplant, the body is better able to withstand the procedure. However, full donor engraftment still takes place, and the desired graft-versus-leukemia effect still occurs.

Outcomes for CMML Patients

CMML is a difficult disease to treat. The recent WHO reclassification of CMML is expected to lead to a greater understanding of this disease and to the development of more effective treatments. All patients are advised to discuss survival information with their physicians. Keep in mind that outcome data can show how other people with CMML responded to treatment, but cannot foretell how any one person will respond.

Many factors influence patient survival. Unfortunately, lasting remissions are not common. The reported median survival of individuals diagnosed with CMML is from 12 to 24 months after the initiation of treatment. In general, statistics may underestimate survival to a small degree since they may not reflect the most recent advance in treatment.

Factors that may indicate a less favorable outcome include

- Severe anemia
- High blast percentage
- High total leukocyte (white cell) count
- High LDH level
- Larger spleen size.

Approximately 20 percent of CMML patients have disease that progresses to acute myelogenous leukemia (AML).

Juvenile Myelomonocytic Leukemia (JMML)

JMML is an uncommon blood cancer. It is a clonal disorder, which means that it begins with one or more changes (mutations) to the DNA of a single cell that multiplies uncontrollably. JMML mostly occurs in infancy and early childhood. It is similar in some ways to adult chronic myelomonocytic leukemia (CMML) in that, with both JMML and CMML, the change takes place in a type of white cell called a “monocyte.”

Monocytes represent about 5 to 10 percent of the cells in normal human blood. These cells and other white cells called “neutrophils” are the two major microbe-eating and microbe-killing cells in the blood. When monocytes leave the blood and enter the tissues, they can attack invading organisms and help combat infection and assist other blood cells, such as lymphocytes, in carrying out their immune functions.

JMML has been known by other names, such as juvenile chronic myelogenous leukemia, chronic granulocytic leukemia, CMML of childhood, chronic and subacute myelomonocytic leukemia and infantile monosomy 7 syndrome.

JMML cells accumulate in the bone marrow and other organs, crowding out normal healthy cells and interfering with the production of sufficient numbers of healthy blood cells such as white blood cells, red blood cells and platelets.

JMML Incidence

JMML accounts for approximately 1.5 percent of childhood leukemia cases. The median age at diagnosis is 2 years. The disease occurs most commonly in infants and children younger than 6 years. JMML is rarely diagnosed in newborns but many patients are diagnosed at between 3 and 12 months. JMML is more prevalent in males than in females by a ratio of 2.5 to 1.

Signs and Symptoms of JMML

The International JMML Working Group includes the following signs and symptoms in their diagnostic criteria for JMML:

- Enlarged liver, enlarged spleen and/or enlarged lymph nodes
- Pallor
- Fever
- Rash.

Other symptoms and signs that have been described are developmental delay, decrease in appetite, irritability and dry cough.

Diagnosis of JMML

Before JMML is diagnosed, other potential diagnoses are usually considered, especially if a child is older than 6 years. For example, CMML, discussed in the first part of this fact sheet, may occur in children under 6 years. Also, although chronic myelogenous leukemia (CML) rarely occurs in children younger than 5 years, it represents about 3 percent of childhood leukemia cases in children aged 15 years or younger.

The tests used to diagnose JMML include blood tests and bone marrow aspiration and biopsy to check for additional signs and symptoms, including cytogenetic abnormalities, such as

- A persistent elevated monocyte count in the blood (greater than 1,000/microliter [1,000/µl] of blood)
- The absence of the Philadelphia chromosome (Ph chromosome) and the *BCR-ABL* gene rearrangement. The Ph chromosome is an abnormality of chromosome 22 found in the marrow and blood cells of patients with CML
- Less than 20 percent blasts in the blood or bone marrow.

Some patients may also have

- Moderate to severe anemia (low red cell counts) and thrombocytopenia (low platelet counts)
- Increased white cell counts (not more than 100,000/µl).

About 50 percent of JMML patients have certain red blood cell changes including

- Higher levels of hemoglobin F than is normal for the age of the patient
- Low levels of carbonic anhydrase (an enzyme)
- Expression of the i antigen on the surface of the red cells.

About 85 percent of JMML patients may have a cytogenetic abnormality. Some of the cytogenetic abnormalities that have been noted in JMML patients include

- Monosomy 7 and other chromosome 7 abnormalities, which occur in approximately 25 to 30 percent of patients
- Abnormalities involving chromosomes 3 and 8, which occur in 5 to 10 percent of cases
- Mutations of the *RAS* family of genes, which occur in about 25 percent of patients
- Mutation of the *NF1* gene. About 30 percent of JMML patients have the *NF1* gene mutation and about 14 percent of JMML patients are also diagnosed with neurofibromatosis 1. In other words, although neurofibromatosis 1 is associated with the *NF1* gene mutation, not all children with the *NF1* gene mutation develop neurofibromatosis 1. Neurofibromatosis 1 is a rare genetic condition associated with coffee-colored spots and pea-sized tumors on the skin, freckling in skin areas not exposed to the sun, optic glioma (a tumor on the optic nerve that affects eyesight), and developmental abnormalities in the nervous system, muscles and bones. A child with neurofibromatosis 1 has about a 500-fold increased risk of developing JMML or another myeloid disorder.
- Mutation of the *PTPN11* gene, which occurs in about 35 percent of patients. The genetic cause for Noonan syndrome is a mutation of the *PTPN11* gene. Children with JMML who have the *PTPN11* gene mutation may have features associated with Noonan syndrome. These typically include heart malformation, short stature, learning disabilities, indentation of the chest, impaired blood clotting and facial changes.

For additional information about lab and imaging tests, please see the free LLS booklet *Understanding Lab and Imaging Tests.*

Treatment of JMML

Parents are advised to

- Seek treatment from a physician who is experienced in treating JMML or from a physician who is in consultation with a center or physician who has experience treating this disease
- Speak with their child's physician about the most appropriate treatment.

Without treatment, JMML progresses rapidly. There are two widely used JMML treatment protocols. They are

- The Children's Oncology Group (COG) JMML Study in North America
- The European Working Group of MDS and JMML in Childhood (EWOG-MDS) Study.

Neither of these studies has developed an internationally accepted treatment protocol for JMML.

Drug Therapy for JMML. Standard chemotherapy, regardless of the intensity, has proven effective only to a small number of patients. 13-*cis*-retinoic acid (Accutane®) has shown some responses leading to disease stabilization and partial remission rather than complete remission.

Stem Cell Transplantation for JMML. Allogeneic stem cell transplantation (giving the patient stem cells from either a related or unrelated matched donor) has been widely used in the treatment of JMML patients. Although this treatment has been noted to achieve long-term survival in up to 50 percent of patients, relapses occur in up to 30 to 40 percent of patients after transplantation. Nonetheless, allogeneic stem cell transplantation remains the only known cure for JMML.

Second transplants have been beneficial for some patients, especially when used in conjunction with reduced immunosuppression, presumably leading to a stronger graft-versus-leukemia effect. On the other hand, donor lymphocyte infusions have proven ineffective in treating JMML patients who have relapsed after undergoing stem cell transplantation.

For additional information on stem cell transplantation, please see the free LLS booklet *Blood and Marrow Stem Cell Transplantation.*

Clinical Trials for JMML

Patient participation in clinical trials is important in order to develop new and better treatments. Parents should talk to their child's physician about whether taking part in a clinical trial would be a good treatment option for their child.

Examples of therapies currently under study to achieve longer-lasting remissions for JMML patients are listed here.

Etanercept (Enbrel®) blocks the hormone called the "tumor necrosis factor" (TNF), which has been shown to play a role in helping the growth of JMML cells. This drug has been approved for the treatment of rheumatoid arthritis and juvenile rheumatoid arthritis. Studies are trying to determine its effectiveness in the treatment of relapsed JMML patients.

Tipifarnib (Zarnestra®) is a type of drug called a "farnesyl transferase inhibitor" that may stop the growth of JMML cells by blocking the enzymes necessary in the mechanisms of cancer cell growth. This drug has demonstrated significant clinical effectiveness according to a clinical trial conducted by the Children's Oncology Group.

Second Stem Cell Transplantation. Clinical trials are studying the effectiveness of second allogeneic stem cell transplantation in JMML patients who have relapsed after a first transplant. For more information on this therapy, see *Stem Cell Transplantation* for JMML on page 9.

Outcomes for JMML Patients

Parents of JMML patients are advised to discuss survival information with their child's physician. Keep in mind that outcome data can show how other children with JMML responded to treatment, but cannot foretell how any one child will respond.

The treatment of JMML patients has not led to long-lasting remissions in most cases. However, there are individual factors that influence patient outcome. In general, the outlook for JMML patients is not as good as it is for patients with other childhood blood cancers; for example, acute leukemias, chronic myelogenous leukemia and lymphoma.

The median survival of JMML patients is less than 2 years. It is important to note that these statistics may underestimate survival to a degree since the data may include outcomes for patients who did not receive treatment.

Factors that may indicate a less favorable outcome include

- Age less than 2 years
- Low platelet count
- Elevated hemoglobin F levels.

There have been a few cases of children under the age of 1 year with Noonan syndrome and a *PTPN11* gene mutation where the disease has improved spontaneously. Similarly, spontaneous improvement of other JMML patients with *RAS* mutations has also been noted.

We're Here to Help

The Leukemia & Lymphoma Society (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 you, visit our Web site, www.LLS.org, or contact

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LLS also provides fact sheets and booklets that can be ordered via the 800 number or through **Free Materials** on the Web site.

Other Resources

The JMML Foundation
(858) 243-4651
www.jmmlfoundation.org
Offers information and resources for JMML patients and their families

The Children's Tumor Foundation
(800) 323-7938
www.ctf.org
Offers information and resources for children with neurofibromatosis

National Cancer Institute (NCI)
(800) 422-6237 or (800) 4-CANCER
www.cancer.gov
Part of the National Institutes of Health, NCI functions as a national resource center for information and education about all forms of cancer, including CMML and JMML.

References

Chronic myelogenous leukemia and related disorders. In: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, eds. *Williams Hematology*. 7th ed. New York, NY: McGraw-Hill Book Company; 2006:1261-1268.

Emanuel PD. Juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia. Spotlight Review. *Leukemia.* 2008;22:1335-1342.

FS-17 December 2008