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

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

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Highlights

- Chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) are uncommon blood cancers that are classified by the World Health Organization (WHO) as “myelodysplastic/myeloproliferative neoplasms.”
- For CMML, the median age at diagnosis ranges from 65 to 75 years. Common CMML symptoms include weakness, fatigue, unexplained bruising, bleeding, infection, enlarged liver and spleen. Most CMML patients are treated with drug therapy. Allogeneic stem cell transplantation is a potential curative option for some patients.
- JMML is most commonly diagnosed in infants and children younger than 6 years. Common JMML symptoms include a pale appearance, developmental delays, decrease in appetite, irritability, enlarged abdomen, dry cough, rash, enlarged liver and spleen and enlarged lymph nodes. Most JMML patients are treated with an 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.

Introduction

The World Health Organization (WHO) has classified chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) as “myelodysplastic/myeloproliferative neoplasms.” CMML and JMML are uncommon blood cancers that have characteristics of two other types of blood cancers called “myelodysplastic syndromes” (MDS) and “myeloproliferative neoplasms” (MPNs).

Myelodysplastic syndromes are a group of diseases in which immature blood cells in the bone marrow do not mature and become healthy blood cells. Myeloproliferative neoplasms are a group of diseases in which the bone marrow makes too many red blood cells, platelets or certain white blood cells.

One of the major advances in the last 5 years is a better understanding of the molecular abnormalities that cause these diseases. This new knowledge is expected to lead to new and improved therapeutic treatments.

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

Chronic Myelomonocytic Leukemia (CMML)

CMML is a clonal disorder, in which a group of identical cells, sharing a common ancestry, multiply uncontrollably. In CMML, the change affects the normal development of a type of white blood 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 tissue, they are converted to macrophages. Macrophages are the monocytes-in-action: they can combat infections in the tissues, ingest dead cells and assist other cells, such as lymphocytes, in carrying out their immune functions.

Monocytes arise from immature blood-forming cells called “stem cells.” In CMML, too many stem cells become monocytes. Some of these stem cells never become mature white blood cells. These immature white blood cells are called “blasts.” Over time, the monocytes accumulate in the marrow and in other organs and interfere with the normal production of other types of blood cells, including red blood cells (which carry oxygen to all the tissues of the body) and platelets.
(which form clots to help stop bleeding after an injury).

The WHO categorizes CMML into the following two subtypes based on the percentage of blast cells found in the blood and bone marrow:

- CMML-1—Less than 5 percent blasts circulating in the blood and less than 10 percent blasts present in the bone marrow
- CMML-2—More than 5 but less than 20 percent blasts circulating in the bloodstream or 10 up to 20 percent blasts present in the bone marrow.

In most healthy people, there are no blasts present in the blood, and less than 5 percent in the bone marrow.

**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 condition in which blood lacks adequate healthy red blood cells to carry sufficient oxygen throughout the body.)
- 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 white blood cell count)
- Enlargement of the spleen and liver
- A 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 cannot usually be confirmed with a single lab test result that shows abnormal blood counts. The diagnosis can only be confirmed after a patient has been monitored, over time, with repeated lab tests and the results are evaluated to rule out other forms of MDS and MPNs.

Findings from a blood smear and a bone marrow aspiration and biopsy are required to make the diagnosis of CMML.

The doctors will be looking for the following findings:

- A persistent elevated monocyte count in the blood (greater than 1,000/monocytes per microliter of blood [1,000/µl] of blood)
- No evidence of a Philadelphia chromosome (seen in a similar disease known as “chronic myeloid leukemia” (CML). This can be determined based on a blood test looking for a particular abnormality known as a BCR/ABL fusion gene.
- Increased numbers of eosinophils (a type of white blood cell). If the eosinophil count is elevated, it is also recommended that the patient is tested for genetic changes involving platelet growth factors.
- Less than 20 percent blasts in the blood and bone marrow. Blasts include myeloblasts, monoblasts and promonocytes (types of immature white blood cells).
- Abnormalities in one or more types of precursor cells that develop into red blood cells, certain types of white blood cells or platelets. These abnormalities are referred to as “dysplasia” which means abnormal growth of cells.
  - If dysplasia is not identified, the diagnosis of CMML may still be made if a clonal molecular or cytogenetic abnormality is identified or if there is a persistent monocytosis (an increased number of monocytes circulating in the blood) for at least 3 months and no evidence of other causes of monocytosis.

**Genetic Mutations**

Approximately 30 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, sometimes the translocation involves the PDGFR-β and TEL genes. Patients who have the PDGFR-β and TEL gene mutations may respond favorably to treatment with the drug imatinib mesylate (Gleevec®). See Drug Therapy for CMML on page 3. An extra copy of chromosome 8 is the most frequently observed cytogenetic abnormality in CMML. This abnormality is associated with a poor prognosis.

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 hematologist/oncologist who is experienced in treating CMML or from a hematologist/oncologist who is in consultation with a cancer center

• Discuss with their doctor the most appropriate treatment for their situation.

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 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. These drugs are known as "hypomethylating agents," and they affect the way genes are controlled. They seem to help stop abnormal cells in the bone marrow from dividing into new cells, and they make these abnormal cells more susceptible to death. Long-term outcome studies have shown that these agents are effective in some patients with CMML.

The small number (about 1 to 4 percent) of CMML patients who have the **PDGFR-β** and **TEL** gene mutations (see **Diagnosis of CMML** on page 2) are treated with the drug imatinib mesylate (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 also approved to treat chronic myeloid leukemia (CML) and some other diseases.

**Stem Cell Transplantation for CMML**

Allogeneic stem cell transplantation has been used to treat, and sometimes cure, CMML patients. The increased use of lower-conditioning regimens and the use of alternative donors, such as cord blood and haploidentical donors, have increased the availability of stem cell transplantation for all patients including those with CMML. The long-term overall survival rate following stem cell transplant is approximately 40 percent. The major cause of failure is relapse. In addition, some patients may develop chronic graft-versus-host disease which can decrease quality of life. See **Treatments Under Investigation** below for more information.

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

**Treatments Under Investigation**

Patients are encouraged to explore, and enter if they are eligible, clinical trials. Clinical trials test new drugs and treatments before they are approved by the US Food and Drug Administration (FDA) as standard treatments. Many of these new drugs and treatments are supported by LLS research programs.

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 CMML 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 booklet **Understanding Clinical Trials for Blood Cancers** at www.LLS.org/booklets or visit www.LLS.org/clinicaltrials.

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

• Decitabine (Dacogen®) and azacitidine (Vidaza®) are being studied for use in combination with other agents such as hydroxyurea, volasertib, and birinapant for CMML patients who have not responded to treatment or who have relapsed after initial therapy.

• 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. Patients also receive immunosuppressive drugs to prevent rejection of the donor cells.

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 will be better able to withstand the procedure, but full donor engraftment still takes place and the desired graft-versus-leukemia effect...
still occurs. Relapse is one of the major causes of failure of stem cell transplant for CMML, and clinical trials are currently evaluating combination therapy with azacitidine, lenalidomide, and donor lymphocyte infusions.

Outcomes for CMML Patients

All patients are advised to discuss survival information with their doctors. Keep in mind that outcome data can only show how other people with CMML responded to treatment, but cannot predict how any one person will respond.

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

Many factors influence patient survival. Factors that may indicate a less favorable outcome include

- Severe anemia
- A high percentage of blasts in the blood and in the bone marrow
- A high total leukocyte (white blood cell) count
- A high level of lactate dehydrogenase (LDH) in the blood
- A high absolute lymphocyte count.

Approximately 20 percent of CMML patients’ conditions progress to acute myeloid leukemia (AML).

Juvenile Myelomonocytic Leukemia (JMML)

JMML is an uncommon blood cancer. It is a clonal disorder, in which a group of identical cells, sharing a common ancestry, multiply uncontrollably. JMML mostly occurs in infancy and early childhood. It is similar in some ways to adult chronic myelomonocytic leukemia (CMML); in both JMML and CMML, the change takes place in an early progenitor cell leading to increased numbers of a type of white blood 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 infections and assist other blood cells, such as lymphocytes, in carrying out their immune functions.

In JMML, too many stem cells become monocytes. Some of these stem cells never become mature white blood cells. These immature white blood cells are called “blasts”. Over time, JMML has been known by other names, such as “juvenile chronic myeloid 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 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 enlarged lymph nodes
- Pale appearance
- Fever
- Rash.

Other symptoms and signs that have been described are developmental delay, decrease in appetite, irritability, dry cough, fatigue, weight loss, recurrent infections, abdominal pain, and bone and joint pain.

Diagnosis of JMML

Before JMML is diagnosed, other potential diagnoses are usually considered, especially if a child is older than 6 years. For example, although chronic myeloid 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.

The diagnosis of JMML requires the following:

- A persistent elevated monocyte count in the blood (greater than 1,000 monocytes per microliter of blood [1,000/µl])
Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML) Facts

- 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 circulating in the blood and present in the bone marrow.

And at least 2 of the following criteria:

- Higher levels of hemoglobin F than is normal for the age of the patient
- Immature myeloid precursors in the blood
- Increased numbers of white blood cells (but not more than 100,000 white blood cells per microliter of blood [100,000/µl]).
- Clonal cytogenetic abnormalities including monosomy 7
- Granulocyte-macrophage colony-stimulating factor (GM-CSF) hypersensitivity of myeloid progenitors.

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 patients
- Mutations of the RAS family of genes, which occur in about 25 percent of patients
- Mutation of the NFI gene. About 30 percent of JMML patients have the NFI gene mutation and about 14 percent of JMML patients are also diagnosed with 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 also 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 hematologist/oncologist who is experienced in treating JMML or from a hematologist/oncologist who is in consultation with a cancer center
- Speak with their child’s doctor about the most appropriate treatment.

Without treatment, JMML progresses rapidly. There are two widely used JMML treatment protocols. They have been developed by:

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

Neither of these protocols has become an internationally accepted treatment for JMML.

Stem Cell Transplantation for JMML

Allogeneic stem cell transplantation has been widely used in the treatment of JMML patients, and it remains the only known cure for JMML. 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. While the rates of relapse are high, patients may achieve a cure with a second stem cell transplant. Second transplants have been beneficial for some patients, especially when used in conjunction with reduced immunosuppression, resulting in 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.

Drug Therapy for JMML

Standard chemotherapy, regardless of the intensity, has proven effective in only a small number of patients. Treatment with 13-cis-retinoic acid (Accutane®) has shown some responses leading to disease stabilization and partial remission (rather than complete remission). Farnesyl transferase inhibitors are a class of drugs that are currently undergoing testing.
as treatment for JMML. Since JMML is difficult to treat with current chemotherapy, participating in a clinical trial investigating new drugs may be an option for children who cannot have a stem cell transplant.

**Treatments Under Investigation**

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

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 JMML 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 booklet *Understanding Clinical Trials for Blood Cancers* at www.LLS.org/booklets or visit www.LLS.org/clinicaltrials.

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 for 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:** the effectiveness of second allogeneic stem cell transplantation in JMML patients who have relapsed after a first transplant is being studied in clinical trials. For more information on this therapy, see *Stem Cell Transplantation for JMML* on page 5.

- **Azacitidine (Vidaza®)** is approved for CMML, and it is also being investigated as a treatment for JMML. It works by changing gene expression patterns in cancer cells and increasing their susceptibility to death.

**Outcomes for JMML Patients**

Parents of JMML patients are advised to discuss survival information with their child’s doctor. Keep in mind that outcome data can show how other children with JMML responded to treatment, but cannot predict 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 myeloid 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 greater than 2 years
- A 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.

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**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 United States and in Canada. To find the chapter nearest to you, visit our Web site at www.LLS.org or contact:
Chronic Myelomonocytic Leukemia (CMML) and Juvenile Myelomonocytic Leukemia (JMML) Facts

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 health care team.

Consult with an Information Specialist. Information Specialists are master’s level oncology social workers, nurses and health educators. They can answer general questions about diagnosis and treatment options, offer guidance and support and assist with clinical-trials searches. 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 Materials. LLS offers free education and support booklets that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/booklets.

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 help cancer patients reach out, share information and provide support. For more information, please visit www.LLS.org/support.

LLS Community. LLS Community is an online social network and registry for patients, caregivers, and supporters of those with blood cancer. It is a place to ask questions, get informed, share your experience, and connect with others. To join visit https://communityview.LLS.org.

Sign Up For an E-newsletter. Read the latest disease-specific news, learn about research studies and clinical trials, and find support for living with blood cancer. Please visit www.LLS.org/signup.

LLS Chapters. LLS offers 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, and other great resources. For more information about these programs or to contact your chapter, please:
- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind.

Clinical Trials (Research Studies). New treatments for patients with CMML/JMML are under way. Many are part of clinical trials. Patients can learn about clinical trials and how to access them. For more information, please:
- Call: (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches.
- Visit: www.LLS.org/clinicaltrials.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please:
- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

Other Resources

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

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

National Cancer Institute (NCI)
(800) 422-6237
www.cancer.gov
The National Cancer Institute (NCI), part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including CMML/JMML. The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trial Registry, at www.cancer.gov/clinicaltrials, where CMML/JMML patients can look for clinical trials.
References


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