

TREATMENT UPDATE:

Chronic Myelogenous Leukemia (CML)

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Chronic myelogenous leukemia (CML) is a form of cancer that originates in the bone marrow, where blood cells are made. In recent years, additional treatment options have become available for people living with CML.

CML is triggered by a chromosomal abnormality (an error during cell growth) in which the ABL gene is mistakenly joined to the BCR gene, forming a mutated BCR-ABL “fusion gene.” The BCR-ABL gene leads to the production of an abnormal protein that fuels the growth of leukemia cells. This chromosomal abnormality is called the Philadelphia (Ph) chromosome.

In CML, there is an uncontrolled growth of both immature and mature myeloid cells (types of white blood cells). The three phases of CML are identified by the number of immature cells (blast cells) in the blood stream:

Chronic. The leukemia is slow-growing and generally responds well to treatment.

Accelerated. The leukemia is growing more quickly and is at higher risk for reaching the blast crisis phase.

Blast crisis. The leukemia is fast-growing and should be treated immediately.

Symptoms of CML can include weight loss, fatigue, fever, night sweats, bone pain and abdominal swelling or discomfort (caused by an enlarged spleen), but many people with CML experience no symptoms. Often, a blood test taken for another reason shows abnormalities such as an increased number of white blood cells. A CML diagnosis is confirmed by looking for the presence of the Ph chromosome through specialized tests or bone marrow samples.

Treatment Options

As CML is a chronic disease, continual monitoring is essential no matter what treatment option is chosen. In the first years after diagnosis, people with CML will see their doctor and other members of their health care team frequently. This typically starts with weekly blood tests, followed by visits every three to six months to assess the response to treatment. Monitoring may consist of complete blood count tests, liver function tests, molecular testing and electrocardiograms to assess heart rhythms.

Targeted Therapy

Targeted therapies are designed to target the specific cell mechanisms that fuel the growth and survival of tumor cells. Tyrosine kinase inhibitors (TKIs), a type of targeted therapy, are used in the treatment of CML. Taken as a pill once or twice daily, TKIs target the protein made by the mutated BCR-ABL fusion gene.

Imatinib (Gleevec), approved by the Food and Drug Administration (FDA) in 2001, was the first TKI used for the treatment of CML. Since then, four other TKIs have been approved: dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif) and ponatinib (Iclusig).

Ponatinib is often used to treat CML that has a specific additional alteration in the BCR-ABL gene known as T315I, which makes CML cells resistant to treatment with other TKIs. Ponatinib can also benefit people whose CML has not gone into remission after several TKI treatments and those with more advanced CML.

CML response is measured in a series of milestones, in which the leukemia volume ideally reduces by certain levels over time. Within three months of TKI treatment, blood counts are expected to be clear of signs of the CML and “early molecular response” is the goal, with BCR-ABL levels falling to 1/10th of their original level. The most important milestone reached with TKI treatments is called “major molecular response” (MMR). MMR occurs when the amount of measurable CML is 1,000 times smaller than when it was first diagnosed. Doctors look for this level of response within the first 12 to 18 months of continuous treatments.

Chemotherapy

Chemotherapy is the use of drugs to destroy cancer cells, usually by stopping the ability of the cells to grow and divide. It is given into a vein using a needle (intravenously) or via a pill or capsule.

Omacetaxine (Synribo) is an injectable chemotherapy used to treat people with CML who are no longer responding to, or could not tolerate, two or more TKIs. Hydroxyurea (Droxia, Hydrea), an older chemotherapy, is often given early in the treatment process when there is an urgent need to lower the number of white blood cells.

For CML that is in the blast crisis phase, treatment often consists of chemotherapy combined with a TKI.

Stem Cell Transplant

A stem cell transplant (also known as a bone marrow transplant) is a procedure in which diseased bone marrow is replaced with healthy bone marrow. When a person with CML receives his or her own stem cells, the procedure is called an “autologous” stem cell transplant. The procedure is known as an “allogeneic” stem cell transplant if the stem cells are from a donor (either a close relative, such as a brother or sister, or a donor from a registry).

In the procedure, stem cells are collected from the patient or the donor. The patient is given high doses of chemotherapy to destroy as many CML cells as possible. In the case of allogeneic transplant, additional medicines are given to prevent rejection. The stem cells are then “infused” (transplanted) into the body, where they travel to the bones and begin rebuilding bone marrow.

Because of the development of TKIs, stem cell transplant is no longer a common treatment approach, but may be an option for younger people, those not responding to TKIs, or those with CML in a more advanced phase.



Taking Your Medication as Prescribed

CML is highly treatable. However, as it is a chronic disease, most people will be on therapy (a TKI) for a minimum of several years, with treatment potentially continuing indefinitely. To gain benefit from TKI therapy, it is extremely important to take the pills daily as prescribed.

You should also continue to take any other prescription or over-the-counter medications as directed by your doctor. An inexpensive pill organizer (available at most drugstores) allows for the sorting of medications by day of week and time of day, which will help you take your medications on schedule. There are also free medication reminder apps available for smart phones or tablets.

Treatment Approaches Being Studied

Additional treatment approaches for CML continue to be studied in clinical trials, including:

Flumatinib. According to results of a phase III trial, flumatinib may have superior effectiveness in the frontline treatment of chronic-phase CML when compared with imatinib. The safety profile of flumatinib continues to be evaluated.

Asciminib. The investigational TKI asciminib is being studied for the treatment of CML, including cases with the T3151 gene mutation, that has not responded to treatment with other TKIs.

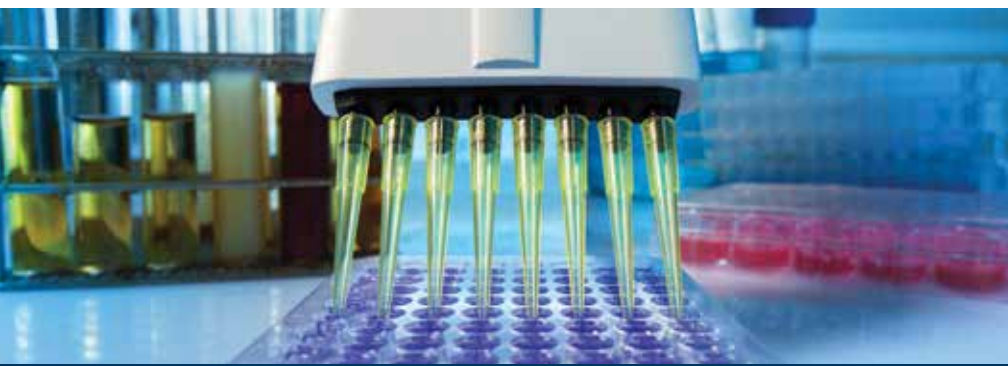
Designed to overcome resistance, asciminib affects a different part of the BCR-ABL protein on leukemia cells. As such, it may be useful in combination with other TKIs as well as a “monotherapy” (a drug used by itself).

PF-114. A phase I trial is evaluating the safety, tolerability and effectiveness of PF-114, a third-generation TKI, in the treatment of resistant forms of CML. PF-114 is an inhibitor of the mutated BCR-ABL gene and is active against Philadelphia chromosome-positive leukemias, and may be effective against the T315I mutation.

HQP1351. HQP1351, a third-generation TKI, has shown potential in a phase I trial as a treatment for TKI-resistant CML. HQP1351 targets a broad spectrum of BCR-ABL mutations, including the T315I mutation. A phase II trial has been initiated.

Combining interferon with other drugs. Before the development of TKIs, the immunotherapy drug interferon was the standard approach in the treatment of CML. Researchers are studying ways of incorporating interferon and a number of other medications designed to strengthen the body’s immune response to CML.

In addition, researchers continue to look for medications to boost the effectiveness of available TKIs and to better understand how to find mutations and causes of TKI resistance.



The Importance of Clinical Trials

Clinical trials are the standard by which we measure the worth of new treatments and the quality of life of patients as they receive those treatments. For this reason, doctors and researchers urge people with cancer to take part in clinical trials.

Your doctor can guide you in making a decision about whether a clinical trial is right for you. Here are a few things that you should know:

- Often, people who take part in clinical trials gain access to and benefit from new treatments.
- Before you participate in a clinical trial, you will be fully informed as to the risks and benefits of the trial, including any possible side effects.
- Most clinical trials are designed to test a new treatment against a standard treatment to find out whether the new treatment has any added benefit.
- You can stop taking part in a clinical trial at any time for any reason.

Treatment Side Effects

All cancer treatments can cause side effects. It is important that you report any side effects that you experience to your health care team so they can help you manage them. Report them right away—don't wait for your next appointment. Doing so will improve your quality of life and allow you to stick with your treatment plan. It's important to remember that not all patients experience all side effects, and patients may experience side effects not listed here.

Side Effects of Targeted Therapy

There are side effects common to all TKIs, including fatigue, diarrhea, nausea, fluid build-up, rash, headache, joint pain, muscle cramps and lowered blood cell counts (especially early in treatment). TKIs can also increase the likelihood of cardiovascular problems, especially for people who already have (or are at risk for) problems of that type.

Side Effects of Chemotherapy

The side effects of chemotherapy depend on the type and dose of drugs given and the length of time they are used, and can include:

- Hair loss
- Increased risk of infection (from having too few white blood cells)
- Easy bruising or bleeding
- Changes in memory or thinking
- Peripheral neuropathy (numbness or tingling in hands and feet)
- Edema (swelling)
- Mouth sores

General Side Effects

Some side effects may occur across treatment approaches. This section provides tips and guidance on how to manage these side effects should they occur.

Managing Digestive Tract Symptoms

Nausea and vomiting

- Avoid food with strong odors, as well as overly sweet, greasy, fried or highly seasoned food.
- Eat meals cold or at room temperature, which often makes food more easily tolerated.
- Nibble on dry crackers or toast. These bland foods are easy on the stomach.
- Have something in your stomach when you take medication to help ease nausea.



Diarrhea

- Drink plenty of water. Ask your doctor about using drinks such as Gatorade, which provide electrolytes.
- Over-the-counter medicines such as loperamide (Imodium A-D and others) and prescription drugs are available for diarrhea but should be used only if necessary and after having a discussion with a member of your health care team.
- Choose fiber-dense foods such as whole grains, fruits and vegetables, all of which help form stools.
- Avoid food high in refined sugar and those sweetened with sugar alcohols such as sorbitol and mannitol.

Loss of appetite

- Eating small meals throughout the day is an easy way to take in more protein and calories, which will help maintain your weight. Try to include protein in every meal.
- To keep from feeling full early, avoid liquids with meals or take only small sips (unless you need liquids to help swallow).
- Keep high-calorie, high-protein snacks on hand such as hard-boiled eggs, peanut butter, cheese, granola bars, liquid nutritional supplements, nuts and canned tuna.
- If you are struggling to maintain your appetite, talk to your health care team about whether appetite-building medication could be right for you.

Managing Fatigue

Fatigue (extreme tiredness not helped by sleep) is one of the most common side effects of many cancer treatments. While the medication being taken may be the main reason, talk to your doctor about additional tests that may be needed to look for other causes. Fatigue can be a symptom of other illnesses, such as anemia, diabetes, thyroid problems, heart disease, rheumatoid arthritis and depression, so be sure to ask your doctor if they think any of these conditions may be contributing to your fatigue.

There are a number of other tips for reducing fatigue:

- Take several short naps or breaks during the day.
- Take short walks or do some light exercise, if possible.
- Try easier or shorter versions of the activities you enjoy.
- Ask your family or friends to help you with tasks you find difficult or tiring.

In some cases, your doctor may lower the dose of the drug, as long as it does not make the treatment less effective. There are also prescription medications that may help, such as modafinil. Your health care team can provide guidance on whether medication is the right approach for your individual circumstances.



Treatment Summaries

A treatment summary, sometimes called a “shadow chart,” is a document you create and which remains in your possession. Maintaining your own records allows you and your family members instant access to the specifics of your diagnosis and treatment. A treatment summary for CML should include:

- Your name and date of birth
- Date of diagnosis
- Name, affiliation and contact information of doctor who gave the diagnosis
- Prescribed therapy/therapies; include dates started and stopped, and dosages when appropriate
- Dates and types of post-diagnosis testing, and the results
- Other medication and supplements you are taking
- Names, affiliations, and contact information of all members of your health care team

Talk to your doctor or a member of your health care team about your intention to create a treatment summary, and ask them what else they suggest be included. Take your treatment summary with you to when you visit any doctor, not just your cancer physician.

Communicating With Your Health Care Team

As you manage your CML, it's important to remember that you are a consumer of health care. The best way to make decisions about health care is to educate yourself about your diagnosis and get to know the members of your health care team, including doctors, nurse practitioners, physician assistants, nurses, dietitians, social workers and patient navigators.

Here are some tips for improving communication with your health care team:

Start a health care journal. Having a health care journal or notebook will allow you to keep all of your health information in one place. You may want to write down the names and contact information of the members of your health care team, as well as any questions for your doctor.

Prepare a list of questions. Before your next medical appointment, write down your questions and concerns. Because your doctor may have limited time, ask your most important questions first and be as specific as possible.

Bring someone with you to your appointments. Even if you have a journal and a prepared list of questions or concerns, it's always helpful to have support when you go to your appointments. The person you bring may also think of questions to ask your doctor or remember details about your symptoms or treatment that you may have forgotten.

Write down your doctor's answers. Taking notes will help you remember your doctor's responses, advice and instructions. If you have a mobile device, ask if you can use it to take notes or record the discussion, which will help you review the information later.

Record your visit if your doctor allows it. Recording the conversation with your doctor gives you a chance to hear specific information again or share it with family members or friends.

Incorporate other health care professionals into your team.

Your cancer physician (medical oncologist, hematologist) is an essential member of your health care team, but there are other health care professionals who can help you manage your diagnosis and treatment:

- Your primary care physician should be kept updated about your CML treatment and any test results.
- If you have (or are at risk for) a cardiovascular problem and are being treated with a TKI, a cardio-oncologist will also be part of your care team.
- Your local pharmacist is a great source of knowledge about the medications you are taking. Have all of your prescriptions filled at the same pharmacy to avoid the possibility of harmful drug interactions.
- Make sure your cancer physician knows of any other medical conditions you have or any pain you are experiencing so that they can consult with your primary care physician or specialists as needed.

Remember, there is no such thing as over-communication.



CancerCare's Free Support Services and Programs

Receiving a diagnosis of CML can be very difficult, and adjusting to the necessary changes in your life can be challenging.

CancerCare® can help. We are a national nonprofit organization providing free, professional services to anyone affected by cancer. Our licensed oncology social workers can provide support and education, help in navigating the complicated health care system and offer information on support groups and other resources.

To learn more about how CancerCare helps, call us at 800-813-HOPE (4673) or visit www.cancercare.org.

You will likely also build your own personal support network, composed of family and friends. In doing so, it's best to take some time to think about the people in your life and how they are best suited to help. Match the task to their strengths—ask a family member who loves to shop to pick up something for you at the store or ask a friend who's a good listener to come over for a chat.

Frequently Asked Questions

Q: I am taking a TKI, but am experiencing side effects. What are my options?

A: For people who experience side effects on a TKI, there are other options—including a brief period off the drug, a dose reduction (either temporarily or for the long term) or a change to another TKI therapy. Any change must be carefully managed under the care of your cancer physician.

Q: Am I more susceptible to infections when being treated for CML?

A: In general, people with CML do not have an increased risk of infection, especially once the CML is in remission. However, both the disease itself and its treatment can impact immune function. When white blood cells are abnormally low (a condition called neutropenia), an infection may progress rapidly and become serious. For this reason, it's important that people being treated for CML immediately report fevers or other signs of infection to their health care team. If neutropenia exists (or if advised by your cancer physician), you should avoid contact with those who have symptoms of a cold and should stay away from crowded places.

The risk of foodborne infection can be reduced by avoiding foods that easily spoil or become moldy without an obvious change in smell or appearance. This includes strawberries and raspberries and soft fruits that lack a thick peel. Undercooked ground beef, poultry and eggs should be avoided during treatment, as should buffets and salad bars.

Q: I'm taking a proton pump inhibitor for GERD. Could this reduce the effectiveness my prescribed TKI?

A: Acid-suppressive drugs such as proton pump inhibitors (PPIs) can reduce the absorption of TKIs into the bloodstream. This effect varies depending on the TKI and the type of acid-suppressive medicine being used. Talk to your cancer physician and the doctor who prescribed the PPI. They may recommend alternative strategies instead of a PPI, or recommend taking the PPI and the TKI several hours apart to minimize interactions.

Q: Should I get a flu shot while being treated for CML?

A: The Centers for Disease Control and Prevention (CDC) recommends seasonal flu shots for people being treated for any form of cancer, including CML. Flu shots are safe for people with compromised immune systems, as they're made from an inactivated virus. The nasal mist form of the flu vaccine should not be taken, as it's made from a live virus. It's also important that family members and close companions of those receiving any type of cancer treatment get flu shots to prevent catching and passing on the flu.

On a related note, ask your doctor or a member of your health care team if you should continue to receive the vaccines recommended for your age and specific situation, such as those for pneumonia, shingles and herpes zoster.



Resources

CancerCare®

800-813-HOPE (800-813-4673)
www.cancercares.org

American Cancer Society

800-227-2345
www.cancer.org

Be The Match® Patient Services

800-627-7692
www.bethematch.org

**Blood & Marrow Transplant
Information Network**

800-597-7674
www.bmtinfonet.org

The Bone Marrow Foundation

800-365-1336
bonemarrow.org

Cancer.Net

Patient information from
the American Society of
Clinical Oncology
888-651-3038
www.cancer.net

CLINICAL TRIALS WEBSITES**EmergingMed**

www.emergingmed.com

National Cancer Institute

www.cancer.gov

Cancer Support Community

888-793-9355
www.cancersupportcommunity.org

**National Bone Marrow
Transplant Link**

800-546-5268
www.nbmtlink.org

National Cancer Institute

800-422-6237
www.cancer.gov

**The Leukemia &
Lymphoma Society**

800-955-4572
www.lls.org

Leukemia Research Foundation

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