LEUKEMIA & LYMPHOMA SOCIETY®

Hairy Cell Leukemia

No. 16 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Hairy cell leukemia (HCL) is a rare, slow-growing leukemia that starts in a B cell (also called B lymphocyte), a type of white blood cell.
- Changes (mutations) in the genes of a B cell can cause it to develop into a leukemia cell. In HCL, leukemic B cells are overproduced and infiltrate the bone marrow and spleen. They may also be found in the liver and lymph nodes. These excess B cells are abnormal and have projections that look like hairs under a microscope.
- Signs and symptoms of HCL include an enlarged spleen and a decrease in normal blood cell counts. Low blood cell counts can result in serious and life-threatening conditions including infections, excessive bleeding and anemia.
- While HCL cannot be cured, great progress in the treatment of HCL has resulted in prolonged survival for many patients. Most patients respond well to treatment with a type of chemotherapy called a purine analog. **Cladribine (Leustatin®)** and **pentostatin (Nipent™)** are purine analogs. **Moxetumomab pasudotox-tdfk (Lumoxiti™)** is FDA approved for adult patients who have relapsed or refractory HCL.
- In spite of great progress in the treatment of HCL, many patients relapse and require additional treatment.

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Introduction

Hairy cell leukemia (HCL) is a rare, slow-growing leukemia that starts in a B cell (B lymphocyte). B cells are white blood cells that help the body fight infection and are an important part of the body's immune system.

Changes (mutations) in the genes of a B cell can cause it to develop into a leukemia cell. Normally, a healthy B cell would stop dividing and eventually die. In HCL, genetic errors tell the B cell to keep growing and dividing. Every cell that arises from the initial leukemia cell also has the mutated DNA. As a result, the leukemia cells multiply uncontrollably. They usually go on to infiltrate the bone marrow and spleen, and they may also invade the liver and lymph nodes. The disease is called "hairy cell" leukemia because the leukemic cells have short, thin projections on their surfaces that look like hairs when examined under a microscope.

When the leukemic hairy cells enter the bone marrow, they affect the production of healthy blood cells. The bone marrow is the soft, sponge-like tissue in the center of most bones where blood cells are made. As the leukemia cells build up in the bone marrow, they suppress the development of other blood cells, including red blood cells, platelets and white blood cells. As a result, there are too few normal functioning blood cells because of too many leukemia cells in the bone marrow. This can cause low blood cell counts, which can lead to anemia, excessive bleeding and/or infections.

HCL is considered a "chronic" leukemia, which means that it often progresses slowly, but it cannot be cured. For many patients, treatment with chemotherapy can lead to remission that can last for years. But in spite of great progress in controlling HCL, many treated patients relapse and require additional therapy.

There is another type of hairy cell leukemia called "hairy cell leukemia variant." HCL variant was previously thought to be a subtype of HCL, but in 2008, the World Health Organization concluded that it was a separate entity from HCL and biologically distinct. HCL variant is rarer than HCL and has a different clinical course and

different treatments. For that reason, this Fact Sheet does not discuss HCL variant. It focuses solely on hairy cell leukemia: its symptoms, diagnosis and treatment.

Incidence and Risk Factors

HCL is an uncommon leukemia. There are approximately 1,000 new cases of HCL in the United States each year.

While the genetic changes that lead to HCL are unknown, there are some factors associated with an increased risk of developing the disease. A "risk factor" is anything that increases a person's chance of being diagnosed with a disease. Having a risk factor, however, does not mean that a person will definitely develop the disease. Some people with several risk factors may never get HCL, while others with no known risk factors may develop the disease. Risk factors associated with HCL include:

- Age. HCL occurs most often in middle-aged to older adults. The median age at diagnosis is about 58 years.
- Gender. More men than women are diagnosed with HCL—it is four times more common in men than in women.
- Exposure to Agent Orange. HCL has been observed in patients following exposure to the herbicide Agent Orange used during the Vietnam War. The National Academies of Sciences, Engineering, and Medicine has concluded in its report titled *Veterans and Agent Orange: Update 2014* that there is sufficient evidence of an association between exposure to Agent Orange and later development of chronic B-cell leukemias and lymphomas, including HCL. As a result, the United States Department of Veterans Affairs considers HCL an illness presumed to be a service-related disability. See *Information for Veterans* on *page 8*.

Signs and Symptoms

The signs and symptoms of HCL are not specific and may resemble those of other, less serious illnesses. It is common for someone with HCL to "not feel well" because of the underproduction of normal blood cells. This happens when the leukemia cells in the bone marrow crowd out the normal blood-making cells. Consequently, patients with HCL may not have sufficient numbers of red blood cells, white blood cells and platelets.

Patients may feel sick because they have:

- Anemia: a decrease in the number of red blood cells
- Thrombocytopenia: a decrease in the number of platelets
- Neutropenia and monocytopenia: a decrease in the number of neutrophils and monocytes, types of white blood cells that fight infection
- Pancytopenia: a decrease in the number of all three white blood cell types: platelets, neutrophils and monocytes

The primary symptoms of the above disorders include:

- Anemia (low red blood cells): Fatigue, paleness, shortness of breath
- Thrombocytopenia (low platelets): Easy bleeding or bruising
- Neutropenia/monocytopenia (low white blood cells): Higher risk of infection
- Pancytopenia (a combination of all of the above symptoms)

Other signs and symptoms of HCL include

- Fever
- Fatigue and weakness
- Shortness of breath
- Unexplained weight loss
- Pain below the ribs, caused by an enlarged, swollen spleen

Diagnosis

This section describes some of the tests that are used to diagnose HCL. Hairy cell leukemia is rare and can be confused with other blood diseases, so it is essential to obtain an accurate diagnosis in order to determine the best treatment options. Therefore, it is important for an experienced doctor to examine the laboratory samples. A doctor who examines lab samples and helps with diagnosis is called a "pathologist"; a pathologist who specializes in blood diseases is called a "hematopathologist."

The initial series of tests should include a medical history and physical examination. If a person has signs or symptoms of leukemia, a hematologist-oncologist will take a thorough medical history. The patient's history

may include information about past illnesses, injuries, treatments and medications. The doctor will want to know about the patient's current symptoms and conduct a physical examination. During the examination, the doctor may listen to the patient's lungs and heart and carefully examine the body for signs of infection and disease. The doctor may feel (palpate) certain areas of the patient's body—such as the armpits and the neck—to check for enlarged lymph nodes. To examine the internal organs, the doctor may also feel other parts of the patient's body. For example, the doctor may palpate the abdomen to see if the patient has an enlarged spleen or liver. Patients with HCL often have an enlarged spleen.

Laboratory Tests. Assessments used to diagnose HCL include

Complete blood count (CBC) with differential. CBC is a test that measures the number red blood cells, platelets and white blood cells in a sample of blood. The "differential" measures the different types of white blood cells in the sample. Usually, people with HCL have low counts of white blood cells, red blood cells and platelets.

Peripheral blood smear. In this test, a sample of blood is viewed under a microscope to count different circulating blood cells, and also to see whether the cells look normal. In patients with HCL, the hematopathologist may observe small- to medium-sized leukemia cells with the presence of hairy-like projections.

Bone marrow aspiration and biopsy. Bone marrow aspiration and biopsy are two procedures used to examine bone marrow cells for abnormalities. These two tests are generally done at the same time. The samples are usually taken from the patient's hip bone (after medicine has been given to numb the skin). Bone marrow has both a solid and liquid part. For a bone marrow aspiration, a special hollow biopsy needle is inserted through the hip bone and into the marrow to remove (aspirate) a liquid sample of cells. For a bone marrow biopsy, a specialized wider needle is used to remove a core sample of solid bone that contains marrow.

For some patients with HCL, a successful bone marrow aspiration at diagnosis is not possible because hairy cells often produce fibrous tissue that scars the bone marrow. The scarring will cause the aspiration to be "dry," meaning a liquid sample could not be obtained.

If an aspirate is not possible, the doctor can examine the bone marrow biopsy for abnormalities. Examination of bone marrow biopsy samples typically show hairy cell infiltrates with increased fibrous tissue. In some patients with HCL, the bone marrow may show hypocellularity, a lower than normal number of blood cells.

Flow cytometry. Flow cytometry is a test used to classify cells based on the type of proteins (markers) on the surface of the cells. Hairy cells have a characteristic surface protein pattern that differs from both healthy B cells and other abnormal (malignant) B cells. The pattern of the surface proteins is called the immunophenotype. There are certain proteins called cluster designations (CDs) that are relatively specific to HCL. In addition to the B-cell antigens CD19, CD20 and CD22, HCL cells also express CD11c, CD25, CD103 and CD123.

Molecular tests. Molecular tests are very sensitive DNA tests that check for specific genetic mutations in cells. In almost all cases of HCL, the leukemia cells have a mutation of the *BRAF V600E* gene. The *BRAF V600E* mutation may serve as a reliable molecular marker to distinguish HCL from other B-cell leukemias and lymphomas.

Some gene mutations may serve as a factor that will help doctors predict the likely outcome of the disease (a prognosis). Approximately 80 to 90 percent of HCL patients have a hypermutation in immunoglobulin heavy chain variable gene called *IGHV*. For example, with conventional chemotherapy, patients who have the *IGHV* mutation have a better prognosis (meaning a more positive outcome) than those without the mutation, who usually have a poorer prognosis (a less favorable outcome).

CT scan. Called a "CAT" scan, this test creates a series of detailed pictures of areas inside the body taken from different angles. The pictures are made by a computer linked to an x ray machine. A dye may be swallowed by or injected into a vein of the patient to help the organs or tissues show up more clearly. CT scans of the chest, abdomen, and/or pelvis may be useful under certain circumstances to examine the size of the spleen, liver and lymph nodes.

Treatment Planning

Various factors affect treatment options and the patient's prognosis—the likely outcome or course of a disease. The results of tests and other variables help predict prognosis. These are called "prognostic factors." Doctors use prognostic factors to help predict how HCL will likely progress in a patient, as well as a patient's probable response to treatment. Some prognostic factors are associated with a lower risk that HCL will return after treatment. These are called favorable risk factors. Other factors are associated with a higher risk that HCL will return after treatment. These are called poor risk factors.

The following signs are associated with a poor prognosis and resistance to purine analog chemotherapy (see *Treatment*, *below*):

- Splenomegaly (>3 cm)
- Leukocytosis (>10 × 10^9/L)
- Hairy cells in the blood (>5 × 10^9/L)
- High $beta_2$ microglobulin (>2N)
- CD38 expression
- Unmutated *IGHV* gene

Every patient's medical situation is different and should be evaluated individually by a hematologist-oncologist who specializes in treating HCL. It is important for patients and their medical teams 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.*

Treatment

A patient has two options for treatment: standard of care or a clinical trial. It is important to talk to the healthcare team about the best treatment option.

HCL is usually slow growing, and not all newly diagnosed patients with HCL require immediate treatment. For approximately 10 percent of patients, if they have stable blood counts and no symptoms at the time of diagnosis, the treatment may be the "watch-and-wait" approach. Watch-and-wait is an appropriate medical approach that means treatment is delayed until signs and symptoms of the disease appear or progress. Some patients with HCL live for many years without any symptoms and without receiving any treatment. Frequent monitoring, including blood testing, is necessary so that treatment can be started if the disease begins to advance.

Patients should begin treatment if they have low blood cell counts (low red blood cell, platelet or white blood cell counts). They should also begin treatment if they exhibit symptoms, including unexplained weight loss, recurrent infections or physical discomfort due to an enlarged spleen and/or liver.

Most often, initial treatment for HCL involves a type of chemotherapy called a purine analog. There are two purine analogs approved by the Food and Drug Administration (FDA) for hairy cell leukemia: **cladribine (Leustatin®)** and **pentostatin (Nipent™)**. These drugs appear to be equally effective in achieving durable remission. The choice between the two drugs is usually determined by doctor preference or patient convenience. Various regimens have been used in clinical trials and the following options are widely accepted:

- Cladribine, administered as continuous intravenous (into a vein, or IV) infusion for 7 days
- Cladribine, administered intravenously (IV) over 2 hours, once per day for 5 days
- Cladribine, injected subcutaneously (under the skin, or SC), once per day for 5 days
- Pentostatin, administered intravenously (IV), once every 2 weeks until remission is achieved

Cladribine and pentostatin both induce durable complete responses in approximately 80 to 85 percent of patients. Most patients who receive cladribine or pentostatin as first-line treatment experience a complete remission that can last for several years. A complete remission means:

- Normalization of blood counts
- Disappearance of hairy leukemia cells from the blood and bone marrow
- Reduction in size of the spleen (determined by physical examination)
- Absence of disease symptoms

Side Effects of Treatment. One side effect of treatment is neutropenia, a condition in which there is a lower-than-normal number of neutrophils, a type of white blood cell that helps fight infections. For HCL patients with neutropenia, doctors may prescribe

a broad-spectrum antibiotic to prevent infections. Sometimes treatment may cause severe neutropenic fever, and if that happens, the doctor may prescribe a granulocyte colony-stimulating factor (G-CSF), a treatment that helps the body produce more white blood cells.

Infection is the most frequent cause of death in HCL patients. Prior to treatment, patients often already have low white blood cell counts, which puts them at risk for infection. Then, after they begin treatment, they are at greater risk for infection because both cladribine and pentostatin are "immunosuppressive," which means they further lower white blood cell counts. This reduces the body's ability to fight infections and other diseases and places patients at higher risk of developing a life-threatening illness.

Doctors should educate patients about preventing infections. It is also important for patients to contact their medical team if they have any signs or symptoms of an infection, such as fever or rash.

Treatment for Patients with Refractory or Relapsed HCL

Treatment with purine analogs has improved survival in HCL patients. Some patients treated with purine analogs achieve remissions that last for years without additional treatments. On the other hand, some patients do not respond to treatment at all, and still others respond at first, but over time their disease relapses and they require additional treatment.

Refractory Disease. Patients whose disease does not respond to primary treatment—or patients who do not achieve a complete response after initial therapy—have what is called refractory HCL. These patients should be encouraged to consider treatment in a clinical trial, if one is available. Other options for patients with refractory disease include

- **Moxetumomab pasudotox-tdfk (Lumoxiti™)**, a CD 22-directed cytotoxin given intravenously, is approved for the treatment of adult patients with relapsed or refractory HCL who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog.
- A different purine analog with or without **rituximab** (**Rituxan®**)
- Rituximab (if the patient is unable to receive purine analog therapy)
- **Interferon alpha** (**Intron® A**)

Relapsed Disease. A disease is said to relapse if it first responded to treatment but then returns. Treatment options for patients who have relapsed disease after remission depend on the quality and duration of the first remission.

- Patients who relapse after a long remission of over five years may be re-treated with the same initial purine analog therapy.
- **Moxetumomab pasudotox-tdfk (Lumoxiti™)**, a CD 22-directed cytotoxin given intravenously, is approved for the treatment of adult patients with relapsed or refractory HCL who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog.
- Patients with remissions that have lasted between two and five years may benefit from additional treatment with the same purine analog, possibly combined with **rituximab** or a clinical trial.
- If the remission lasted for less than two years, options include
  - Treatment with alternative purine analog with **rituximab**
  - Rituximab (if the patient is unable to receive a purine analog)
  - Diagnostic testing to reconfirm HCL diagnosis
    - If HCL is confirmed, treatment with alternative therapies, including agents in a clinical trial. See *Treatments Under Investigation, below*.

Treatments Under Investigation

Great progress in the treatment of patients with HCL has resulted in high remission rates and prolonged survival for many patients. However, research continues because there is still not a cure for HCL, and many patients do relapse at some point after treatment.

Clinical Trials. Every new drug or treatment regimen currently available goes through a series of studies called "clinical trials" before it becomes a part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians and researchers to

ensure as much safety and scientific accuracy as possible.

Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. When appropriate, Information Specialists refer patients for personalized clinical-trial navigation by trained nurses, which is available through our Clinical Trial Support Center.

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

Research Approaches. Some classes of novel therapies and drugs under investigation include:

- **BRAF Inhibitors.** Recent data have shown that almost all patients with HCL have a mutation of the *BRAF V600E* gene. This gene makes a protein called BRAF, which causes some cancer cells to grow and divide. **Vemurafenib (Zelboraf®)** is a BRAF inhibitor that stops cells from producing the BRAF protein. Vemurafenib is currently approved by the FDA for the treatment of melanoma, and is now being used in clinical trials in patients with relapsed and refractory HCL. Complete remissions have been reported after using vemurafenib in patients with relapsed and refractory HCL. The dose and duration of treatment remains to be determined in clinical trials. Additionally, newer targeted inhibitors of BRAF such as **dabrafenib (Tafinlar®)** also show promise in relapsed disease.
- **B-cell Receptor Inhibitors.** Abnormal signaling of the B-cell receptor pathway has been linked to B-cell malignancies. Bruton's tyrosine kinase (BTK), a protein in this pathway, plays an important role in the growth and survival of malignant B cells. The BTK inhibitor **ibrutinib (Imbruvica®)** may stop the growth of cancer cells by blocking some of the enzymes that stimulate malignant B cells to grow and divide uncontrollably. Ibrutinib has been approved for treating patients with certain relapsed or refractory B-cell malignancies, and researchers are studying ibrutinib—alone or in combination with the drug rituximab—as a treatment for refractory/relapsed HCL.
- **Monoclonal Antibody Therapy.** Monoclonal antibody therapy is a type of targeted treatment that uses drugs or other substances to identify and attack specific types of cancer cells but it causes less harm to normal cells than chemotherapy. Clinical trials are exploring the use of the monoclonal antibody **rituximab (Rituxan®)**, alone or in combination with other drugs, for the treatment of HCL. Hairy cells, like most B cells, express CD20. Rituximab works by targeting the CD20 antigen on normal and malignant B cells. Then the body's natural immune defenses are recruited to attack and kill the marked B cells.
- **Immunotoxins.** Immunotoxins are a class of anticancer drugs that link monoclonal antibodies and toxins. The monoclonal antibodies are designed to attach to the surface of the leukemia cells and deliver the toxins to kill the cells. **LMB-2 immunotoxin** is in clinical trials to study the response rate in patients with recurrent or refractory CD25-positive HCL. This immunotoxin is made up of two parts: a genetically engineered monoclonal antibody that binds to cancer cells with CD25 on their surface, and a bacteria-produced toxin that kills the cancer cells to which LMB-2 binds.

Long-Term Follow-Up

Hairy cell leukemia is considered a chronic form of cancer because it never completely goes away. Periodic medical examinations for patients in complete remission are important. Patients should have their blood counts checked routinely to ensure that they are still in remission. If blood counts begin to decline, patients need to discuss treatment options with their doctors.

Acknowledgment

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Farhad Ravandi, MD
Janiece and Stephen A. Lasher Professor of Medicine
Chief, Section of Developmental Therapeutics
Department of Leukemia
University of Texas – MD Anderson Cancer Center
Houston, TX

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/chapterfind or contact:

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573

Call 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 entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

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, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/informationspecialists
- Visit: www.LLS.org/informationspecialists

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. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

Free Information Booklets. LLS offers free education and support booklets that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

- Call: (877) 557-2672
- Visit: www.LLS.org/copay

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

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

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations by a registered dietitian with experience in oncology nutrition. Consultants assist callers about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition for more information.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients to reach out and share information. Please visit www.LLS.org/chat for more information.

Podcast. Listen in as experts and patients guide listeners in understanding diagnosis and treatment, and suggest resources available to blood cancer patients. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Visit www.LLS.org/TheBloodline for more information and to subscribe.

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

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. Please visit www.LLS.org/resourcedirectory for more information.

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

Information for Veterans. Veterans with HCL who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/agentorange.

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period. For more information, please

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter "depression" in the search box

Feedback. To give suggestions about this booklet, visit www.LLS.org/PublicationFeedback.

Other Resources

Hairy Cell Leukemia Foundation
www.hairycellleukemia.org
(224) 355-7201

The Foundation is dedicated to improving outcomes for patients by advancing research into the causes and treatment of HCL and by providing educational resources and comfort to all those affected by HCL. The website includes access to publications from experts and a list of centers of excellence, leading institutions and medical professionals around the world working to advance the treatment and understanding of HCL.

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