Understanding Chronic Lymphocytic Leukemia

CLL, the second-most common form of blood cancer, is being tested for more often and diagnosed earlier, and with new treatments, the quality of life for patients is vastly improved.

By Jim Trageser

Chronic lymphocytic leukemia (CLL) is one of the least publicized forms of cancer in the popular media, despite being the second-most common form of leukemia, which is referred to as cancer of the blood. Those who develop CLL usually do not have symptoms in the early stages. Patients diagnosed with this disease are usually in their middle years or older. However, patients as young as in their 20s and 30s may develop this type of illness. The most common age bracket for developing CLL are people in their 60s and 70s. It is thought that this disease may be more prominent in older people because the bone marrow (where blood cells are made) may not be as effective as it was in earlier years.

The National Institutes of Health reports that people of Eastern European or Jewish descent are more likely to develop CLL than are others.[1] And, while it represents about one-third of all cases of leukemia, CLL is still relatively rare: Only about one in 200 people in the United States will develop CLL in their lifetime, with about 16,000 new cases diagnosed each year.[2]

What Is CLL?

CLL tends to progress more slowly[3] than other forms of leukemia, hence the word "chronic" in its name. In fact, CLL patients can be affected unknowingly with this illness for several years due to its slow-growing nature.

CLL affects the lymphocyte cell line. This cell line belongs to the white blood cell group, which plays an important role in fighting infection. CLL develops from the B cell origin of lymphocytes, as opposed to the T cell

lymphocytes. B cells help fight infection; T cells are "killer" cells. Without the proper function of B cells, one's body cannot properly fight infections. Consequently, someone with CLL has an impaired immune system and can be at risk for more infections.

As with all forms of leukemia, CLL originates in the bone marrow, the spongy interior of bones where all blood cells are created. The blood cells start out as hematopoietic stem cells (immature cells that have not yet determined their cell line maturation), and further develop into mature blood cell lines such as platelets, red blood cells and the group of white blood cells. CLL affects the stem cell line that has been designated to form into mature B cells. But, due to the development of this disease, the lymphocytes grow out of control and accumulate in the bone marrow and blood, where they crowd out healthy blood cells.

Although CLL is a slow-growing cancer, it is best known for overcrowding the bone marrow and entering the peripheral blood system. Since blood cell production in the bone marrow needs to remain in constant balance, the overproduction of white blood cells causes a disturbance in other cell lines. Patients may exhibit forms of anemia, as well as high lymphocyte counts that can be detected in a complete blood count (CBC) test that detects the overabundant CLL cells proliferating out of balance.

Since CLL is a cancer of the B cell lymphocytes, it also can affect the lymphatic system and infiltrate lymph nodes, the spleen and other organs.[4] The lymphatic system is, along with the bloodstream, part of the circulatory system that carries lymphatic fluid, which is a key part of the body's immune system. When infiltration occurs, patients are diagnosed with "bulky disease," meaning that they have palpable lymph nodes and other organs that have been infiltrated with the disease. CLL that is confined to the bone marrow is not considered "bulky disease" and is usually diagnosed at earlier stages.

Symptoms of CLL

As mentioned, CLL develops slowly and with today's advanced medical diagnostic tools, it is often dianosed before any symptoms appear. Those patients who do exhibit symptoms may experience any of the following: enlarged lymph nodes, swollen abdomen, fatigue, excessive sweating, changes in appetite, recurring infections, sudden weight loss, fever and excessive bruising (generally late in the disease's development).[1] Fatigue is one of the most common, chronic symptoms patients with CLL will battle daily. Patients may have frequent infections (colds, bronchitis) diagnosed.

Many physicians today routinely check blood work on their patients, especially in older ages. A CBC with differential can help lead to the diagnosis of CLL.

Causes of CLL

At present, medical researchers do not know what causes most cases of CLL. It does not appear to be the type of cancer that is caused by inherited DNA mutations, and so it is likely the product of DNA damage acquired after birth. Yet, close relatives of those with CLL are more likely to develop it than are others.[6]

In addition, environmental factors may be a risk factor for developing this disease. For example, people who were exposed to the herbicide Agent Orange, used in the Vietnam War to clear jungle, tend to have a higher risk of developing CLL.

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There also are some suggestions that long-term exposure to other pesticides and herbicides may raise the risk, particularly among farmers, ranchers and agricultural workers, but this is still being studied.[6] Interestingly, radiation exposure, smoking and other common risk factors known to be associated with other cancers do not seem to be tied to CLL.[1]

To summarize, the major risk factors for CLL are advanced age (most cases develop in patients over 70 years of age) and ethnicity (Eastern European and Jewish people are most likely to develop the disease). It is extremely rare in Asia. Men also are slightly more likely to develop CLL than women,[7] but the reason for this disparity is not understood.

Diagnosing CLL

Until the last 20 years, most CLL cases were not diagnosed until noticeable symptoms had arisen,[8] which indicates progression of disease. Today, with many geriatricians and

general practitioners ordering blood work for their elderly patients, CLL can be diagnosed in its earliest stages.

People with CLL may display many different symptoms. Some may be anemic due to overcrowding of the bone marrow that doesn't allow the red blood cell line to develop and mature. Patients may have infiltrated lymph nodes, therefore presenting with palpable lymph nodes. Patients may have a swollen abdomen due to spleen or liver involvement. But the most common complaint is fatigue; this is due to the many effects CLL has on the body and blood cells.

If a physician suspects a patient may have CLL or other blood-related cancers, a variety of tests can be ordered to determine the diagnosis. The first test to be performed is a CBC.[9] In this test, the number and types of blood cells are counted and compared with what a healthy person should have. If patients have too many lymphocytes in their blood work, then CLL may be suspected. Usually, a decrease in red blood cells and/or platelets also will be reported. The physician may add another blood test called LDH, which can indicate the presence of CLL. The physician will then order a bone marrow biopsy to confirm the diagnosis. After taking a small piece of bone and marrow (where blood cells grow), the specimens are stained to indicate normal and abnormal cells. Then they are sent to a pathologist who will look at the cells under a microscope to confirm if the bone marrow has abnormal cells, such as abnormal lymphocytes — identifying a diagnosis of CLL.

Treatment for CLL

Once patients are diagnosed with CLL, the next step is to determine if it has spread. This is known as "staging,"[1] and those who have had a friend or relative with cancer are familiar with the terms "stage 1 cancer" or "stage 4 cancer" (stage 1 being the earliest form, and stage 4 indicating the cancer has spread). As additional tests are ordered, samples may be taken from the lymph nodes, bone marrow or spinal fluid to see if and how far the cancer has spread. The doctor also may order a CT scan to look for infiltration into lymph nodes in the abdomen and spleen.

Early-stage CLL is typically treated with observation. If the CLL has progressed, or if there are complications (repeated infections or indications that a rare but aggressive form of CLL is present), chemotherapy may be prescribed. Radiation is generally not the first line of therapy for eradicating CLL, but it may be used to help fight infiltrated lymph nodes or other tissue where CLL cells have implanted.

Fludarabine is a chemotherapy drug that interferes with DNA's ability to reproduce itself.[10] (DNA is the molecule that contains all of a person's genetic information; when a cell divides, it must first make an identical copy of its DNA so each of the two new cells will have all the genetic information of the original cell.) Since cancerous cells reproduce so much more rapidly than healthy cells, the drug has more of an impact on the cancerous cells than healthy ones. The drug also tends to stay in the bloodstream, so it does not affect other tissues very much.[10] This is a very well-tolerated drug and is usually used in the first line of therapy.

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Another drug called Rituxan, which is a monoclonoal antibody, is widely used to fight CLL. Rituxan is able to attack cells that are CD20+. These cells include CLL cells. Since Rituxan can "find" CD20+ cells, it is a well-tolerated drug because it only affects those cells. Rituxan is commonly used in conjunction with Fludarabine. The combination of these two drugs has shown to be extremely effective in treating CLL.

A chemotherapy drug called Leukeran (chlorambucil) also may be given, although it has mostly been replaced by Fludarabine. Leukeran is an alkylating agent, which attaches an extra molecule to a cell's DNA, so the cell can no longer divide and reproduce. Again, this affects cancerous cells more than healthy ones.

Cytoxan is also an alkylating agent, working similarly to Leukeran. Cytoxan is generally used in combination with Fludarabine and Rituxan in patients with advanced bulky disease. These drugs together have been shown to be one of the most effective treatments for CLL.

All of these drugs also may be prescribed in combination, along with blood transfusions, to provide healthy white blood cells to increase patients' immunological defenses.

Alemtuzumab, known as Campath, also targets CLL cells. This monoclonal antibody targets cells that exhibit CD23+ antigens. Through advances in science, we have learned that CLL cells specifically can display this antigen, therefore only CLL cells are targeted and irradiated. Campath is usually used as a second line of therapy, although studies are being conducted to determine

whether Campath in combination with other drugs can achieve a first remission.

Bendamustine is another chemotherapy agent that may be prescribed. It works by creating cross-strands between DNA strands so that cells cannot reproduce.[14]

The compromised immune system caused by CLL can be assisted in fighting infection with vaccines or regular immunoglobulin (IG) therapy. These treatments help the body restore its ability to fight infection. And, patients undergoing chemotherapy will have the typical side effects that accompany use of the various drugs. Since B cells express IG (the most abundant form of globulin found in the blood that helps fight infections) and CLL affects B cells, intravenous IG replacement therapy is usually necessary to boost the immune system to help keep the patient from acquiring multiple infections.

The only currently available treatment considered to provide a cure (which is no evidence of disease for five years or more) is a bone marrow transplant or stem cell transplant. Transplants may be attempted if a remission has been achieved.[1]

Managing the Disease

Since the only cure for CLL is a bone marrow transplant or stem cell transplant, and patient selection for this therapy can be limited due to the potential side effects, most people with CLL will live with the disease for the rest of their lives. Patients who still have evidence of disease but no symptoms can be considered in "remission" but not cured.

About half of all patients diagnosed in early stages of CLL will live more than 12 years.[1] Given the typical age at which CLL appears, many of those patients will die of a cause other than CLL. Many patients with early-stage CLL will live years with the disease with no treatment other than regular follow-up visits with their doctor, and with few changes in their lifestyles.

All patients with CLL, even those in remission, will want to maintain frequent, regular contact with their doctors.[15]

Looking Ahead

There are numerous new approaches in treatment now in clinical trials or earlier research that offer hope of improved treatment and even nonsurgical cures for CLL. From programming the body's own T cells (one type of infection-fighting white blood cells) to attack and destroy cancerous cells, to using genetic therapies to cause the body to reject cancerous cells, progress is being made by researchers on several fronts.[16] Other possibilities include targeting proteins that are unique to cancerous cells. All of these treatments offer the promise of more effective means of slowing the development and spread of CLL, and some may lead to an actual cure.

Currently, CLL patients can live a normal life and have minimal, if any, side effects from the newest treatments available. As treatments improve their efficiency in fighting CLL, and supporting therapies like IG treatment strengthen patients' ability to fight infections, the quality of life for patients diagnosed with CLL continues to improve. ◪

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