Hematologic Neoplasms Leukemia

Signs and symptoms

Damage to the bone marrow, by way of displacing the normal bone marrow cells with higher numbers of immature white blood cells, results in a lack of blood platelets, which are important in the blood clotting process. This means people with leukemia may easily become bruised, bleed excessively, or develop pinprick bleeds (petechiae).

White blood cells, which are involved in fighting pathogens, may be suppressed or dysfunctional. This could cause the patient's immune system to be unable to fight off a simple infection or to start attacking other body cells. Because leukemia prevents the immune system from working normally, some patients experience frequent infection, ranging from infected tonsils, sores in the mouth, or diarrhea to life-threatening pneumonia or opportunistic infections.

Finally, the red blood cell deficiency leads to anemia, which may cause dyspnea and pallor.

Some patients experience other symptoms, such as feeling sick, having fevers, chills, night sweats, feeling fatigued and other flu-like symptoms. Some patients experience nausea or a feeling of fullness due to an enlarged liver and spleen; this can result in unintentionalweight loss. Blasts affected by the disease may come together and become swollen in the liver or in the lymph nodes causing pain and leading to nausea.

If the leukemic cells invade the central nervous system, then neurological symptoms (notably headaches) can occur. All symptoms associated with leukemia can be attributed to other diseases. Consequently, leukemia is always diagnosed through medical tests.

The word *leukemia*, which means 'white blood', is derived from the disease's namesake high white blood cell counts that most leukemia patients have before treatment. The high number of white blood cells are apparent when a blood sample is viewed under a microscope. Frequently, these extra white blood cells are immature or dysfunctional. The excessive number of cells can also interfere with the level of other cells, causing a harmful imbalance in the blood count.

Some leukemia patients do not have high white blood cell counts visible during a regular blood count. This less-common condition is called *aleukemia*. The bone marrow still contains cancerous white blood cells which disrupt the normal production of blood cells, but they remain in the marrow instead of entering the bloodstream, where they would be visible in a blood test. For an aleukemic patient, the white blood cell counts in the bloodstream can be normal or low. Aleukemia can occur in any of the four major types of leukemia, and is particularly common in hairy cell leukemia.

Causes

No single known cause for any of the different types of leukemia exists. The known causes, which are not generally factors within the control of the average person, account for relatively few cases. The different leukemias likely have different causes.

Leukemia, like other cancers, results from mutations in the DNA. Certain mutations can trigger leukemia by activating oncogenes or deactivating tumor suppressor genes, and thereby disrupting the regulation of cell death, differentiation or division. These mutations may occur spontaneously or as a result of exposure to radiation or carcinogenicsubstances.

Among adults, the known causes are natural and artificial ionizing radiation, a few viruses such as human T-lymphotropic virus, and some chemicals, notably benzene and alkylating chemotherapy agents for previous malignancies. Use of tobacco is associated with a small increase in the risk of developing acute myeloid leukemia in adults.

Cohort and case-control studies have linked exposure to some petrochemicals and hair dyes to the development of some forms of leukemia. A few cases of maternal-fetal transmission have been reported. Diet has very limited or no effect, although eating more vegetables may confer a small protective benefit.

Viruses have also been linked to some forms of leukemia. Experiments on mice and other mammals have demonstrated the relevance of retroviruses in leukemia, and human retroviruses have also been identified. The first human retrovirus identified was human T-lymphotropic virus, or HTLV-1, which is known to cause adult T-cell leukemia.

Some people have a genetic predisposition towards developing leukemia. This predisposition is demonstrated by family histories and twin studies. The affected people may have a single gene or multiple genes in common. In some cases, families tend to develop the same kinds of leukemia as other members; in other families, affected people may develop different forms of leukemia or related blood cancers.

In addition to these genetic issues, people with chromosomal abnormalities or certain other genetic conditions have a greater risk of leukemia. For example, people with Down syndrome have a significantly increased risk of developing forms of acute leukemia (especially acute myeloid leukemia), and Fanconi anemia is a risk factor for developing acute myeloid leukemia.

Whether non-ionizing radiation causes leukemia has been studied for several decades. The International Agency for Research on Cancer expert working group undertook a detailed review of all data on static and extremely low frequency electromagnetic energy, which occurs naturally and in association with the generation, transmission, and use of electrical power.

They concluded that there is limited evidence that high levels of ELF magnetic (but not electric) fields might cause childhood leukemia. Exposure to significant ELF magnetic fields might result in twofold excess risk for leukemia for children exposed to these high levels of magnetic fields. However, the report also says that methodological weaknesses and biases in these studies have likely caused the risk to be overstated. No evidence for a relationship to leukemia or another form of malignancy in adults has been demonstrated.

Since exposure to such levels of ELFs is relatively uncommon, the World Health Organization concludes that ELF exposure, if later proven to be causative, would account for just 100 to 2400 cases worldwide each year, representing 0.2 to 4.9% of the total incidence of childhood leukemia for that year (about 0.03 to 0.9% of all leukemias).

According to a study conducted at the Center for Research in Epidemiology and Population Health in France, children born to mothers who use fertility drugs to induce ovulation are more than twice as likely to develop leukemia during their childhoods than other children.

Race is known to play a role, with some racial groups being more at risk than others. Hispanics, especially those under the age of 20, are at the highest risk for leukemia, whilewhites, Native Americans, Asians, and Alaska Natives are at higher risk than blacks.

In the case of gender, more men than women are diagnosed with leukemia and die from the disease. Around 31 percent more men than women live with leukemia.

Diagnosis

Diagnosis is usually based on repeated complete blood counts and a bone marrow examination following observations of the symptoms, however, in rare cases blood tests may not show if a patient has leukemia, usually this is because the leukemia is in the early stages or has entered remission. A lymph node biopsy can be performed as well in order to diagnose certain types of leukemia in certain situations.

Following diagnosis, blood chemistry tests can be used to determine the degree of liver and kidney damage or the effects of chemotherapy on the patient. When concerns arise about visible damage due to leukemia, doctors may use an X-ray, MRI, or ultrasound.

These can potentially view leukemia's effects on such body parts as bones (X-ray), the brain (MRI), or the kidneys, spleen, and liver (ultrasound). Finally, CT scans are rarely used to check lymph nodes in the chest.

Treatment

Most forms of leukemia are treated with pharmaceutical medication, typically combined into a multi-drug chemotherapy regimen. Some are also treated with radiation therapy. In some cases, a bone marrow transplant is useful.

Acute lymphoblastic Leukemia

Management of ALL focuses on control of bone marrow and systemic (whole-body) disease. Additionally, treatment must prevent leukemic cells from spreading to other sites, particularly the central nervous system (CNS) e.g. monthly lumbar punctures. In general, ALL treatment is divided into several phases:

- *Induction chemotherapy* to bring about bone marrow remission. For adults, standard induction plans include prednisone, vincristine, and an anthracycline drug; other drug plans may include L-asparaginase or cyclophosphamide. For children with low-risk ALL, standard therapy usually consists of three drugs (prednisone, L-asparaginase, and vincristine) for the first month of treatment.
- *Consolidation therapy* or *intensification therapy* to eliminate any remaining leukemia cells. There are many different approaches to consolidation, but it is typically a high-dose, multi-drug treatment that is undertaken for a few months. Patients with low- to average-risk ALL receive therapy with antimetabolite drugs such as methotrexate and 6-mercaptopurine (6-MP). High-risk patients receive higher drug doses of these drugs, plus additional drugs.
- *CNS prophylaxis* (preventive therapy) to stop the cancer from spreading to the brain and nervous system in high-risk patients. Standard prophylaxis may include radiation of the head and/or drugs delivered directly into the spine.
- *Maintenance treatments* with chemotherapeutic drugs to prevent disease recurrence once remission has been achieved. Maintenance therapy usually involves lower drug doses, and may continue for up to three years.
- Alternatively, *allogeneic bone marrow transplantation* may be appropriate for high-risk or relapsed patients.

Chronic lymphocytic Leukemia

Hematologists base CLL treatment on both the stage and symptoms of the individual patient. A large group of CLL patients have low-grade disease, which does not benefit from treatment. Individuals with CLL-related complications or more advanced disease often benefit from treatment. In general, the indications for treatment are:

- Falling hemoglobin or platelet count
- Progression to a later stage of disease
- Painful, disease-related overgrowth of lymph nodes or spleen
- An increase in the rate of lymphocyte production

CLL is probably incurable by present treatments. The primary chemotherapeutic plan is combination chemotherapy with chlorambucil or cyclophosphamide, plus a corticosteroidsuch as prednisone or prednisolone.

The use of a corticosteroid has the additional benefit of suppressing some related autoimmune diseases, such as immunohemolytic anemia orimmune-mediated thrombocytopenia. In resistant cases, single-agent treatments with nucleoside drugs such as fludarabine pentostatin, or cladribine may be successful. Younger patients may consider allogeneic or autologous bone marrow transplantation.

Acute myelogenous

Many different anti-cancer drugs are effective for the treatment of AML. Treatments vary somewhat according to the age of the patient and according to the specific subtype of AML. Overall, the strategy is to control bone marrow and systemic (whole-body) disease, while offering specific treatment for the central nervous system (CNS), if involved.

In general, most oncologists rely on combinations of drugs for the initial, *induction phase* of chemotherapy. Such combination chemotherapy usually offers the benefits of earlyremission and a lower risk of disease resistance. *Consolidation* and *maintenance* treatments are intended to prevent disease recurrence. Consolidation treatment often entails a repetition of induction chemotherapy or the intensification chemotherapy with additional drugs. By contrast, maintenance treatment involves drug doses that are lower than those administered during the induction phase.

Chronic myelogenous

There are many possible treatments for CML, but the standard of care for newly diagnosed patients is imatinib (Gleevec) therapy. Compared to most anti-cancer drugs, it has relatively few side effects and can be taken orally at home. With this drug, more than 90% of patients will be able to keep the disease in check for at least five years, so that CML becomes a chronic, manageable condition.

In a more advanced, uncontrolled state, when the patient cannot tolerate imatinib, or if the patient wishes to attempt a permanent cure, then an allogeneic bone marrow transplantation may be performed. This procedure involves high-dose chemotherapy and radiation followed by infusion of bone marrow from a compatible donor. Approximately 30% of patients die from this procedure.

Hairy cell

Patients with hairy cell leukemia who are symptom-free typically do not receive immediate treatment. Treatment is generally considered necessary when the patient shows signs and symptoms such as low blood cell counts (e.g., infection-fighting neutrophil count below 1.0 K/µL), frequent infections, unexplained bruises, anemia, or fatigue that is significant enough to disrupt the patient's everyday life.

Patients who need treatment usually receive either one week of cladribine, given daily by intravenous infusion or a simple injection under the skin, or six months of pentostatin, given every four weeks by intravenous infusion. In most cases, one round of treatment will produce a prolonged remission.

Other treatments include rituximab infusion or self-injection with Interferon-alpha. In limited cases, the patient may benefit from *splenectomy* (removal of the spleen). These treatments are not typically given as the first treatment because their success rates are lower than cladribine or pentostatin.

T-cell prolymphocytic

Most patients with T-cell prolymphocytic leukemia, a rare and aggressive leukemia with a median survival of less than one year, require immediate treatment.

T-cell prolymphocytic leukemia is difficult to treat, and it does not respond to most available chemotherapeutic drugs. Many different treatments have been attempted, with limited success in certain patients: purine analogues (pentostatin, fludarabine, cladribine), chlorambucil, and various forms of combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone CHOP, cyclophosphamide, vincristine, prednisone [COP], vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, bleomycinVAPEC-B).

Alemtuzumab (Campath), a monoclonal antibody that attacks white blood cells, has been used in treatment with greater success than previous options.
Some patients who successfully respond to treatment also undergo stem cell transplantation to consolidate the response.

Juvenile myelomonocytic

Treatment for juvenile myelomonocytic leukemia can include splenectomy, chemotherapy, and bone marrow transplantation.