FEATURE ARTICLE

The Disease With Hope:
Hairy Cell Leukemia

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Hairy cell leukemia (HCL), comprising 2% of all leukemias, is a chronic disorder characterized by mononuclear cells with prominent cytoplasmic projections. For years, patients with HCL underwent splenectomies and then interferon alpha for treatment, which provided high response rates but low percentages of complete remission. More recent treatments with 2-chlorodeoxyadenosine result in 85%–90% complete remission, minimal toxicity, and lower rates of relapse using a single course of therapy. A second course of therapy can be administered if HCL continues to be resistant or recurs. New research using anti-CD22 recombinant immunotoxin BL22 is proving successful. With these latest chemotherapy options, patients' prognoses are optimistic.

Hairy cell leukemia (HCL) first was described in 1958 by Bouroncle, Wiseman, and Doan, who called it leukemic reticuloendotheliosis. In 1966, Schrek and Donnelly changed the name to hairy cell leukemia, describing its unique appearance. The hairy cell is a B lymphocyte; little is known about its pathology (Goodman, Burian, Koziol, & Saven, 2003). HCL accounts for 2% of all leukemias, and 600 new cases are diagnosed each year. Men are four times more likely to be diagnosed with HCL than women, and the mean age of onset is 52 years. HCL occurs primarily in Caucasians; Jewish men are overrepresented (Goodman, Bethel, et al., 2003).

At a Glance

- Hairy cell leukemia (HCL) is a rare form of leukemia.
- Early symptoms include fatigue, infection, and bleeding.
- Treatment with 2-chlorodeoxyadenosine is used for initial pharmacologic management of HCL.

Background

HCL is a monoclonal proliferation of relatively mature B lymphocytes, typically expressing monoclonal immunoglobin G on their cell surfaces and having unique immunoglobulin gene arrangement. Hairy cells also coexpress the pan B-cell antigens CD19, DC20, and CD22 (Goodman, Bethel, et al., 2003). B lymphocytes in adults are processed in bone marrow and manufacture antibodies. Each B lymphocyte has on the surface of its cell membrane 100,000 antibody molecules that react specifically to one type of antigen. With the disruption of the B lymphocyte in HCL, immunity is disturbed and infections are common (Guyton, 1991).

Serum levels of soluble interleukin-2 (IL-2) are high in HCL and correlate with disease activity. The abnormal cells do not produce IL-2; however, they do produce tumor necrosis factor and a B-cell growth factor (Goodman, Bethel, et al., 2003).

The cause of HCL is unknown. Genetic and viral origins have been studied without any associations noted. Patients with HCL have been found to have a higher previous occupational exposure to ionizing radiation and organic chemicals (Goodman, Bethel, et al., 2003).

Signs and Symptoms

Early signs and symptoms of HCL are related to pancytopenias, including fatigue, infection, and, less commonly, bleeding. All HCL cases present with anemia; 75% of patients have thrombocytopenia (Schroeder, Tierney, McPhee, Papadakis, & Krupp, 1992). Splenomegaly can be massive in 90% of patients and hepatomegaly occurs in 40%, both causing abdominal discomfort (Goodman, Bethel, et al., 2003). HCL is progressive, with a median survival rate of 53 months, if left untreated (Saven & Piro, 1994).

Identification and Diagnosis

The hairy cell is mononuclear with prominent cytoplasmic projections, irregular cytoplasmic outlines, and villi of various lengths. They are relatively large cells with abundant pale blue cytoplasm and a low nuclear and cytoplasmic ratio. Hairy cells may be identified by Wright's stained peripheral blood films in approximately 90% of patients. The cells appear as round, oval,

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(Submitted April 2006. Accepted for publication August 18, 2006.)

Digital Object Identifier: 10.1188/07.CJON.731-735

dumbbell-shaped, convoluted, or even multilobated nuclei. In contrast to a normal lymphocyte's clumped chromatin, HCL chromatin is stippled and nucleoli are absent or inconspicuous (Ravandi & O'Brien, 2005) (see Figure 1).

Examination of bone marrow is imperative for positive identification of HCL. Bone marrow aspirates usually are unsuccessful. Dry taps occur as a result of increased reticular fibers; therefore, a bone core biopsy should be performed. In the bone marrow, hairy cells have the appearance of a fried egg (Ravandi & O'Brien, 2005). The cells possess abundant water, spacing the individual nuclei, which look to be bland (i.e., pale stained) and slightly larger than the lymphocytes. Mitoses of hairy cells are rare or absent. Mast cells commonly are noted and prominent (Bitter, 1992). In bone marrow, hairy cells have a characteristic histochemic staining pattern in which their high activity of tartrate-resistant acid phosphatase allows for an accurate diagnosis (Goodman, Bethel, et al., 2003).

In the liver, portal and sinusoidal infiltration by hairy cells is noted. Hairy cells line anglomastoid channels, where erythrocytes accumulate, causing lesions and destruction of the sinusoidal wall. Lymph nodes are affected in only 5%–10% of patients, causing peripheral lymphadenopathy of 2 cm or more (Bitter, 1992).

On autopsy, hairy cells have been noted in kidney, colon, stomach, myocardium, meninges, adrenal, pancreas, and connective tissue. Bone complications may cause pain related to osteolytic lesions of the axial skeleton; the proximal femur is the most common site (Bitter, 1992).

Complications

Infection occurs in a third of patients with HCL at diagnosis and is a major cause of morbidity and mortality. Septicemia and pneumonia account for 80% of fatalities from infections by gram-negative bacilli in patients with HCL. Fever in patients with HCL always should be considered to be caused by infection unless proven otherwise (Hoffman & Rai, 1996). Vasculitis has been observed in 10% of patients, affecting small vessels and resulting in arthralgias and skin lesions. Second malignancies have been observed in 22% of patients who have HCL (Goodman, Burian, et al., 2003). In a study by Federico et al. (2002), an increased incidence of secondary malignancies with HCL could not be confirmed.

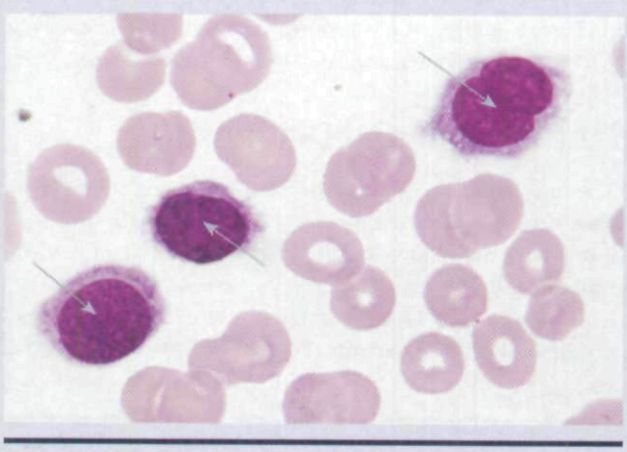

Figure 1. Hairy Cell Leukemia Cells

Note. Photo courtesy of Michael Abbey/Photo Researchers, Inc. Used with permission.

Drug Therapies and Supportive Care

Patients with HCL begin treatment when they become symptomatic with significant neutropenia, anemia, thrombocytopenia, symptomatic splenomegaly, fever or night sweats, or recurrent serious infections (Goodman, Bethel, et al., 2003). For a comparison of common treatments for HCL, see Table 1. The most current, successful drug used in the treatment of HCL is 2-chlorodeoxyadenosine (2-CdA), a purine nucleoside analog that passively crosses the cell membrane of certain normal and malignant lymphocyte and monocyte populations. Researchers theorize that 2-CdA is toxic selectively to cells with high deoxycytidine kinase and low deoxynucleotides, impairing the ability to repair single strands of DNA. The broken ends of DNA cause disruption of cellular metabolism. Impairment of DNA synthesis also is noted with interference of the division of cells (Kastrup, 2004).

For patients with normal renal functioning, 0.1 mg per kilogram of body weight per day of 2-CdA is given by continuous infusion for seven days. While targeting the hairy cells, 2-CdA also causes immunosuppression by decreasing B- and T-lymphocyte counts. Careful hematologic monitoring for worsening neutropenia, anemia, and thrombocytopenia is recommended, particularly during the first four to eight weeks after treatment because of bone marrow suppression. In a clinical trial (Kastrup, 2004), mild nausea also was documented in 28% of patients treated with 2-CdA and rashes occurred in 27%.

In 1990, the first 12 patients received 2-CdA at the Scripps Clinic and Research Foundation. Eleven of the patients achieved a complete response and one a partial response. Degrees of remission were defined as follows: complete remission (an absence of hairy cells), partial remission (from 1%–5% of abnormal cells), and minor response (5% of abnormal cells or greater) (Seymour, Kurzrock, Freireich, & Estey, 1994). Several days after initial treatment, the total leukocyte count of these patients decreased; hairy cells rapidly decreased as well. Hemoglobin levels, neutrophil levels, and platelet counts returned to normal within eight weeks. Bone marrow examination confirmed that complete remission was achieved. None of the eleven patients relapsed in the first four years. Although antibiotics were given, culture-negative leukopenia febrile episodes were related to the rapid disappearance of circulating hairy cells and shrinkage of spleen size (Piro, Carrera, Carson, & Beutler, 1990).

Relapse after complete remission is defined as the reappearance of hairy cells in the peripheral-blood smear and/or bone marrow. In a study by Goodman, Burian, et al. (2003), 95% of patients achieved a complete response and 5% partial response. After a median time of 42 months, 37% of the patients relapsed. A second course of 2-CdA was given, resulting in complete response for 75% of patients, partial response for 17%, and a failed response for 8%. Thirty-three percent of the patients experienced a second relapse; of these 10 remaining patients, a third dose of 2-CdA was administered with a 60% complete response. In 1998, the same group of patients who received three doses of 2-CdA had an overall survival rate of 96% at 48 months (Goodman, Burian, et al.).

Table 1. Drug Therapies for Hairy Cell Leukemia

MEDICATION	DOSAGE	ADVERSE EFFECTS
2-chlorodeoxyadenosine	0.1mg/kg continuous infusion for seven days	Immunosuppression, worsening neutropenia, anemia and thrombocytopenia, mild nausea, and rashes
Deoxycoformycin	4 mg/m^2 every other week for three to six months	Life-threatening central and peripheral nervous system, renal, and hepatic toxicity; nausea; vomiting; fever; photosensitivity; and keratoconjunctivitis
Anti-CD22 recombinant immunotoxin BL22	0.2–4.0 mg diluted in 50 ml of 0.2% albumin in normal saline for 30 minutes via IV infusion every other day for a total of three doses	Cytokine-release syndrome and life-threatening hemolytic uremic syndrome
Rituximab	375 mg/m^2 once a week for four weeks	Allergic reactions, myelosuppression, and depletion of lymphocytes

Note. Based on information from Goodman, Bethel, et al., 2003; Kastrup, 2004; Kreitman et al., 2001; Ravandi & O'Brien, 2005.

Deoxycoformycin (DFC), which binds tightly to adenosine deaminase, is another HCL treatment. DFC is important in the development or survival of normal T and B lymphocytes and prevention of lymphopenia. The course of treatment with DFC is 4 mg/m^2 every other week for three to six months until the maximal response is attained. Complete response rates range from 44%–89%. When compared with disease-free survival rates of 2-CdA, no difference exists statistically between the two agents when used as initial treatments (Ravandi & O'Brien, 2005). Side effects can be life threatening and include central and peripheral nervous system, renal, and hepatic toxicity. At lower doses, symptoms are less severe and include nausea, vomiting, fever, photosensitivity, and keratoconjunctivitis (Goodman, Bethel, et al., 2003).

The most recent treatment for 2-CdA–resistant HCL is anti-CD22 recombinant immunotoxin BL22, a recombinant immunotoxin containing an anti-CD22 variable domain monoclonal antibody RFB4. BL22 is a bioengineered chemotherapy made by cloning portions of antibodies to truncated *Pseudomonas* endotoxin. Doses from 0.2–4.0 mg should be diluted in 50 ml of 0.2% albumin in normal saline and administered as a 30-minute IV infusion every other day for a total of three doses. When BL22 trialed for other cancers, caution was advised (Kreitman et al., 2001). Toxicities noted included cytokine-release syndrome and life-threatening hemolytic-uremic syndrome (Ravandi & O'Brien, 2005). Infliximab and rofecoxib are given in conjunction with BL22 to diminish inflammation of cytokine-release syndrome. Sixty-nine percent of patients achieve complete remission, and 13% achieve partial remission. The most serious side effect of BL22 is a decrease in platelet and red blood cell counts. The clotting and hemolysis of red blood cells may cause transitory renal failure (Kreitman et al.).

Rituximab is another treatment for 2-CdA–resistant HCL, similar to BL22. Rituximab is a monoclonal antibody directed against the pan-B-cell antigen (CD20) and is administered at 375 mg/m^2 once a week for four weeks (Goodman, Bethel, et al., 2003). Common side effects include allergic reactions with fever, chills, angioneurotic edema, and hypotension. Less frequent side effects are myelosuppression and depletion of lymphocytes; in rare cases when rituximab was used for other cancer therapies, cardiac toxicity was observed (Klastersky, 2006). Responses to rituximab and BL22 therapies vary but have shown promise (Goodman, Bethel, et al.).

In the past, splenectomy was the initial treatment of choice for HCL with severe peripheral cytopenias; however, minimal change often occurs in bone marrow postoperatively and patients have progressive disease within 12–18 months (Quade, 2006). With several effective systemic agents now available, splenectomy is no longer the primary treatment (Goodman, Bethel, et al., 2003). Currently, splenectomy is indicated for active or uncontrolled infections, severe thrombocytopenia with severe bleeding, splenomegaly with extreme pain or rupture, and chemotherapy failure.

Partially purified alpha (leukocyte) human interferon (IFN-alpha) first was given for HCL in 1984. However, since the emergence of 2-CdA and its improved outcomes, IFN-alpha has not been used for HCL (Goodman, Bethel, et al., 2003).

Case Study

Mr. M has been a chemist for more than 40 years and has had contact intermittently with organic chemicals throughout his career. A 62-year-old Caucasian man, Mr. M confided that he was having recurring bruising without any trauma on his trunk. A 1 cm circular ecchymotic area above his upper lip also was observed, which he stated kept returning. Mr. M was advised to see a medical practitioner for blood tests. Mr. M also had vague complaints of fatigue, muscle soreness, and abdominal cramping. When he went to his personal physician, blood work was obtained revealing white blood cells at 21,500 mm^3, hemoglobin and hematocrit at 11.8% and 36.5 g/dl, platelets of 50,000 mm^3, and lymphocytes of 67.5%. Splenomegaly was noted during Mr. M's abdominal assessment. His next visit was to a hematologist/oncologist, who performed a bone marrow aspiration and told Mr. M that he most likely had lymphocytic leukemia. Two days later, the bone marrow results were obtained and Mr. M was diagnosed with HCL. Bone marrow aspirations usually are dry with HCL (Ravandi & O'Brien, 2005), but Mr. M's physician was able to obtain a sample.

Mr. M was admitted to the local hospital three days later and received 0.1 mg/kg of 2-CdA by continuous infusion for seven days. On day 5, he developed a fever, mild nausea, and a loss of appetite. Blood cultures, urinalysis, and a urine culture were obtained, and broad-spectrum antibiotics were given via IV. All culture results were negative.

Mr. M was discharged on day 10 with instructions to follow up with his oncologist monthly. Four months after treatment, he had a repeat bone marrow examination. The results for hairy cells were negative. He continued to follow up every three months for six months, then every six months, and remained in complete remission for four years. When Mr. M's white blood cells and platelets began to decline, he was readmitted to the hospital.

Mr. M was given a second treatment of 2-CdA at 0.1 mg/kg by continuous infusion for seven days. His cell counts reacted similarly to the previous treatment.

Twelve years since his diagnosis, Mr. M visits his oncologist yearly. His laboratory results suggest that he will remain in complete remission. However, one year after his last round of chemotherapy, he began experiencing increasing weakness on his left side, which had suffered a subdural hematoma 36 years prior to his diagnosis of HCL. Magnetic resonance imaging was performed and revealed that a quarter of his brain was covered in blood. A computed tomography scan of his head revealed multiple small encapsulated areas of fluid on the right side of his brain. A large amount of blood was evacuated in a craniotomy. Mr. M's physicians believed that the thrombocytopenia from HCL and subsequent 2-CdA caused the previous injury to rebleed. Because of the subdural injury, Mr. M is no longer a candidate for further chemotherapy should the HCL recur.

Advanced Practice Implications

During his course of illness, Mr. M experienced anxiety, despite knowing the excellent prognosis for HCL with 2-CdA treatment. He sought information that would dispel his concerns. Anxiety is a justifiable response to the threatening diagnosis of cancer. Anxiety does not have to be debilitating but rather can promote patients' compliance with treatment regimens. Abnormal anxiety prevalence in patients with cancer ranges from 10%–30% and is defined by symptoms that are not in appropriate proportion to the level of threat. Without intervention, disruption of functioning or emotional distress, including insomnia, will ensue (Stark et al., 2002).

Patients with HCL also have to deal with issues similar to any diagnosis of cancer. Fear, depression, loss of control, and vulnerability may occur at any time during the course of the disease. Nurses should assess patients' support systems and coping mechanisms by encouraging patients and families to verbalize their personal reactions to the present and past situations (Dest, 2000). Mr. M and his wife had to put aside their plans, not knowing what lie ahead. Mrs. M once expressed that she was afraid she would lose her best friend. For months after coping with HCL, Mr. M said he questioned every ache and pain he felt, wondering whether the leukemia had recurred. Consulting the Hairy Cell Leukemia Research Foundation at http//home.earthlink.net/~shanford/hcl.htm on a regular basis assisted Mr. and Mrs. M by providing emotional and informational support.

Because of low white blood cell counts, Mr. M was to told avoid contact with crowds and children who might be contagious. Some of Mr. M's physicians recommended avoiding sick people for a year after treatment. Gutaj (2002) advocated that patients follow up with their oncologists, stressing the need to have blood levels monitored.

HCL is a unique type of cancer because, unlike many other forms, a hope for quantity and quality of life exists. The treatment of 2-CdA provides a high success rate, as well as few side effects and a short time of administration. Mr. M was able to return to work, travel, and continue the life he had before he was diagnosed with HCL with one small exception; he knows to follow up every year with his physician. Should HCL recur, physicians can offer additional successful options, providing Mr. M and his family with confidence and hope for recovery.

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References

Bitter, M.A. (1992). Hairy cell leukemia. In D.M. Knowles (Ed.), *Neoplastic hematopathology* (pp. 1209–1228). Baltimore, MD: Williams and Wilkins.

Bouroncle, B.A., Wiseman, B.K., & Doan, C.A. (1958). Leukemic reticuloendotheliosis. *Blood, 13,* 609–630.

Dest, V.M. (2000). Colorectal cancer. *RN, 63*(3), 54–59.

Federico, M., Zinzani, P.L., Frassoldati, A., Vinceti, M., Mode, A., Annino, L., et al. (2002). Risk of second cancer in patients with hairy cell leukemia: Long-term follow-up. *Journal of Clinical Oncology, 20,* 638–646.

Goodman, G.R., Bethel, K.J., & Saven, A. (2003). Hairy cell leukemia: An update. *Current Opinion in Hematology, 10,* 258–266.

Goodman, G.R., Burian, C., Koziol, J.A., & Saven, A. (2003). Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. *Journal of Clinical Oncology, 21,* 891–896.

Gutaj, D.A. (2000). Lymphoma. *RN, 63*(8), 32–37.

Guyton, A.C. (1991). *Textbook of medical physiology.* Philadelphia: W.B. Saunders.

Hoffman, M., & Rai, K. (1996). Hairy cell leukemia. In E.S. Henderson, T.A. Lister, & M.F. Greaves (Eds.), *Leukemia* (6th ed., pp. 587–594). Philadelphia: W.B. Saunders.

Kastrup, E.K. (Ed.). (2004). Cladribine. In E.K. Kastrup (Ed.), *Drug facts and comparisons* (pp. 1855–1857). St. Louis, MO: Wolters Kluwer Health.

Klastersky, J. (2006). Adverse effects of the humanized antibodies used as cancer therapeutics. *Current Opinion in Oncology, 18,* 316–320.

Kreitman, R.J., Wilson, W.H., Bergeron, K., Raggio, M., Stetler-Stevenson, M., FitzGerald, D.J., et al. (2001). Efficacy of the anti-CD22 recombinant immunotoxin BL22 in chemotherapy-resistant hairy-cell leukemia. *New England Journal of Medicine, 345,* 241–247.

Piro, L.D., Carrera, C.J., Carson, D.A., & Beutler, E. (1990). Lasting remissions in hairy-cell leukemia induced by a single infusion of 2-chlorodeoxyadenosine. *New England Journal of Medicine, 322,* 1117–1121.

Quade, G. (2006). Hairy cell leukemia. Retrieved January 29, 2006, from http://imsdd.meb.uni-bonn.de/cancer.gov/CDR0000062926.html

Ravandi, F., & O'Brien, S. (2005). Chronic lymphoid leukemias other

than chronic lymphocytic leukemia: Diagnosis and treatment. *Mayo Clinic Proceedings, 80,* 1660–1674.

Saven, A., & Piro, L. (1994). Newer purine analogues for the treatment of hairy-cell leukemia. *New England Journal of Medicine, 330,* 691–697.

Schrek, R., & Donnelly, W.J. (1966). "Hairy" cells in blood in lymphoreticular neoplastic disease and "flagellated" cells of normal lymph nodes. *Blood, 27,* 199–211.

Schroeder, S., Tierney, L.M., McPhee, S.J., Papadakis, M.A., & Krupp, M.A. (Eds). (1992). *Current medical diagnosis and treatment.* Norwalk, CT: Appleton and Lange.

Seymour, J.F., Kurzrock, R., Freireich, E.J., & Estey, E.H. (1994). 2-chlorodeoxyadenosine induces durable remissions and prolonged suppression of CD4+ lymphocytes counts in patients with hairy-cell leukemia. *Blood, 83,* 2906–2911.

Stark, D., Kiely, M., Smith, A., Velikova, G., House, A., & Selby, P. (2002). Anxiety disorders in cancer patients: Their nature, associations, and relation to quality of life. *Journal of Clinical Oncology, 20,* 3137–3148.

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