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wenty-five years after it was first described, hairy cell leukemia (HCL) was still killing one-third of all its patients within 5 years. But around that time, researchers hit three home runs. First, an early application of interferon improved survivorship dramatically. Then, in quick succession, two different versions of a class of drugs called nucleoside analogs made further dramatic gains, putting most patients into complete remission. These remissions typically last a decade—and sometimes much longer.

Partly because of that success, HCL is now an orphan in the world of cancer research. Most patients lead fairly normal lives for nearly normal lifespans. Also, HCL is one of the most uncommon cancers; there are just 500–800 new cases in the United States each year, according the Leukemia and Lymphoma Society. That combination removes the urgency that drives young medical researchers to embark on careers in oncology.

In fact, the field is small and actually shrinking, according to Michael R. Grever, M.D., professor of internal medicine at the Ohio State University Medical Center in Columbus. He and other HCL experts have launched a new consortium, which they hope will spur new interest in HCL, raise awareness of important questions that remain unanswered, and erase major gaps in our understanding of the disease.

These questions range from molecular to clinical. Although the prognosis is better than for most other cancers, there is no cure. Some patients eventually relapse, and the drugs lose effectiveness with each successive treatment.

Furthermore, major gaps remain in our understanding of HCL. For example, the normal version of the malignant cell—the hairy cell—is unknown, as are the chemical and biological triggers of HCL. Researchers are ignorant as to why one drug can treat HCL effectively, when most other cancers require multimodalities. Answers to these and other questions might someday lead to actual cures, Grever said.

People with HCL present with the characteristic “hairy” B lymphocytes with their projecting villi, which look like...
the Medusa from Greek mythology or like a sea anemone. They also have low blood counts and often very enlarged spleens.

Hairy cells accumulate in the bone marrow, compromising production of normal white blood cells, red blood cells, and platelets. Patients suffer from infections, fatigue, bruising, weakness, and weight loss, as well as from a discomfiting fullness that prevents eating more than small quantities of food at a time.

**The 1950s**

In the 1950s, clinician researchers recognized different symptoms and complications of HCL in disparate reports. Bertha A. Bouroncle, M.D., of the Ohio State University Medical Center, assembled these clinical snapshots into one disease process in a seminal report that she published in *Blood* in July 1958.

In those days, and for several decades thereafter, splenectomy was a common treatment—not because of any understanding of the spleen’s role in the disease but because its frequently massive proportions suggested that it played an important role. In hindsight, this bought time because “you are debulking the disease, and you also tend to improve blood counts ... because the spleen would destroy good cells,” said John Greer, M.D., professor of medicine and pediatrics and clinical director of hematology and stem cell transplantation at Vanderbilt University Medical Center in Nashville, Tenn.

Interferon first got the attention of clinical researchers in the early 1980s. “Schering [Plough Corp., the drug company] had come to us in late ’82 or early ’83 to do a trial in lymphoma, with recombinant interferon,” said Harvey M. Golomb, M.D., dean of clinical affairs and professor of medical sciences at the University of Chicago Medical Center. “I asked if I could add hairy cell because I had a lot of patients failing after splenectomy and chlorambucil [a drug commonly used prior to that time],” and Schering agreed.

Interferon had strongly suppressed the proliferation in lymphoma cells and had shown antitumor activity in patients with B-cell and T-cell neoplasms, so it seemed logical to try it on HCL. It worked fairly well; interferon rapidly normalized blood counts, resulting in complete remissions in 4%–30% of patients and partial remissions in 43%–86%, said Golomb, citing a large series of studies.

**Nucleoside Analogs**

But then came pentostatin, the first nucleoside analog. Nucleoside analogs interfere with DNA replication because they resemble components of DNA closely enough to be incorporated into the growing chain, but they fail to form all the proper bonds.

Pentostatin was a major improvement over interferon. A comparison trial begun in 1986 showed that at least three-quarters of patients on pentostatin achieved complete remission, compared with 10% on interferon. Long-term follow-up of the 356 patients on pentostatin found 60% still in
remission after 10 years, with close to 80% survival, said Grever.

Nonetheless, clinicians worried that pentostatin would leave patients susceptible to infections. Pentostatin can drive concentrations of CD4 cells—which initiate response to microbial infections—down to levels comparable to those in HIV/AIDS, where they may remain for 9–12 months before climbing back to normal, said Grever. But “patients did not have overwhelming infections with these drugs,” he said.

Treatments with pentostatin was also inconvenient. “Some patients have to come back and forth [between home and hospital, for treatments] every 2 weeks for up to 6 months,” said Grever. But cladribine (2-chlorodeoxyadenosine), a pentostatin look-alike molecule that quickly followed, was more easily administered via one week-long intravenous infusion. It has become first-line treatment. And with cladribine, patients suffered none of the unpleasantness commonly associated with chemotherapy, such as nausea, vomiting, and hair loss, said Golomb. “The patients would ask you if there was really medicine in the bottle,” he said.

But there are other side effects—a higher incidence of fever and double the need for antibiotics after treatment compared with that for pentostatin, said Grever. Cladribine also lowers blood counts and suppresses the immune system, according to Deborah Thomas, M.D., associate professor of medicine at the University of Texas M. D. Anderson Cancer Center in Houston. She added that two patients retreated with cladribine, had residual hairy cells in their bone marrow. Greer said that the eventual relapse rate among patients treated with nucleoside analogs is 30%–40%. The younger the age at diagnosis, the greater is the risk of exhausting treatment options. The median age of diagnosis is in the low 50s, and the youngest patients are diagnosed in their 20s, according to Golomb.

**Monoclonal Antibodies**

Monoclonal antibodies directed at proteins on hairy cells’ surfaces have been developed in the last 20 years, and they are being used both singly and in combination with nucleoside analogs.

Around 1999, some researchers decided to try a regimen of cladribine followed by the monoclonal antibody rituximab to more fully expunge hairy cells from the marrow, said Greer. A study by Giulia Cervetti, of the University of Pisa in Italy, in the October 2008 *British Journal of Haematology*, supported this approach. Among patients who achieved complete remission, 94% were disease free 5 years after treatment, whereas among those who were free of residual hairy cells in the bone marrow, 100% were disease free after 5 years.

Another study, by Paulette Mhawech-Fauceglia, M.D., of the State University of New York at Buffalo and the Roswell Park Cancer Institute, in the March 2006 issue of *Archives of Pathology and Laboratory Medicine*, showed a dose–response curve between the amount of residual disease and the risk of relapse. Relapse rate varied from zero among those with less than 1% hairy cells to three-quarters among those with more than 5% hairy cells.

Those more likely to relapse could receive monoclonal antibodies, said Thomas. Robert Kreitman, M.D., chief of the clinical immunotherapy section in the Laboratory of Molecular Biology at the National Cancer Institute, is conducting a study to compare the benefit of giving the agents simultaneously versus sequentially.

Thomas initially tested rituximab alone because she felt that it was safer than nucleoside analogs, especially after the deaths of the patients on cladribine. “Rituximab doesn’t drop the blood counts by itself or predispose patients to infections,” she said.

Also, unlike nucleoside analogs, monoclonal antibodies don’t damage the marrow stroma—such damage could lead to myelosuppression. “For younger patients who will live for longer periods with the disease, avoiding drugs that could potentially damage the marrow, limiting future therapeutic choices, may be desirable,” said Alan Saven, M.D., head of the division of hematology and oncology at the Scripps Clinic in La Jolla, Calif.

Unlike other treatments for HCL, monoclonal antibodies should be used before there is a high disease burden, said Thomas.

Some monoclonal antibodies do have substantial side effects. BL22, a designer monoclonal antibody that totes a toxic residue, or immunotoxin, to kill the cancer cell, can cause hemolytic uremic syndrome, which reduces kidney function, said Kreitman. However, it has been completely reversible in the HCL patients affected, he said. A new version of this drug, which may mitigate that problem, is undergoing phase I testing in multicenter trials.

**Current Issues**

Despite the field’s success in reducing morbidity and mortality, about 15%–20% of patients still exhaust their treatment options, said John Cawley, M.D., Ph.D., a
professor in the department of hematology at the University of Liverpool in the U.K.

Whereas immunotoxins and other monoclonal antibodies may pick up some of the nonresponders, others will face death. A better understanding of the fundamental biology might lead to superior treatments, and even cures, said Grever.

For example, although the signaling pathways leading to HCL are well mapped, the ultimate trigger is unknown, said Cawley, who is conducting fundamental research into the biology of hairy cells, including their signaling and their interactions with other cells and matrix components. That information “... might yield new therapeutic approaches,” he said.

Despite these intriguing mysteries, attrition in the ranks of HCL researchers is unsettling, said Grever. Of roughly 10,000 abstracts submitted to the American Society of Hematology last year, only three concerned HCL. “There are about 15–20 senior people in the field, but only one or two are under 45. At one point, all of us were under 45. We worry that if we don’t get people interested in this field, we may lose the next generation of experts in this disease,” he said.

To counter this trend, researchers launched the Hairy Cell Consortium at the 50th American Society of Hematology Annual Meeting that took place in San Francisco in December 2008. Its purpose is to provide guidelines to physicians and information for patients and their families and to encourage collaborative research. “Our hope,” Grever said, “is that this consortium will attract the brightest of new hematologists and oncologists to consider this area for future investigation.”