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Making Cancer History™

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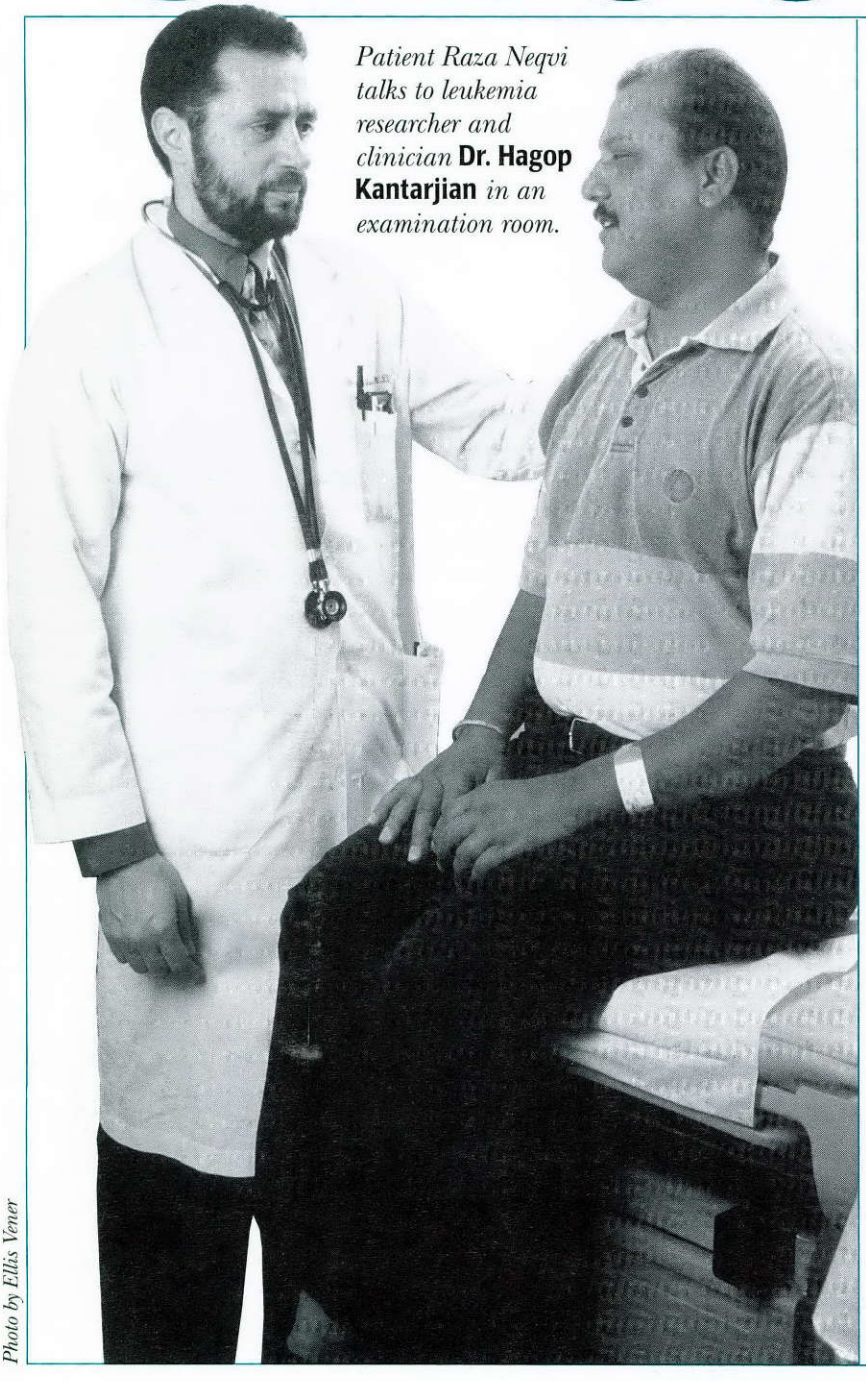

Patient Raza Neqvi talks to leukemia researcher and clinician **Dr. Hagop Kantarjian** *in an examination room.*

Photo by Ellis Vener

New Treatment Strategies Improve Prognosis in Patients with Chronic Leukemias

by Sunita Patterson

Dramatic improvements in the outcome of leukemias over the last two decades are prompting optimism from leukemia specialists.

"There's the potential of reaching high cure rates in many leukemia subsets by the year 2010," said Hagop Kantarjian, M.D., professor of medicine in The University of Texas M. D. Anderson Cancer Center's Department of Leukemia.

Advances include those in chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL). In CML average survival has

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Treatments for Chronic Leukemias

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more than doubled, increasing from three years to seven or eight years, and in CLL the percentage of patients experiencing complete remissions has increased from less than 5% to more than 30%.

Making these advances possible have been improvements in the old approaches and introduction of new ones: new drug therapies and enhanced bone marrow transplantation technology have been combined by researchers with advancing genetic and immune system understanding. The result: improved outcomes.

For CML, traditional cytotoxic chemotherapy alone has proved ineffective in preventing disease progression. CML is characterized by three phases: an indolent or chronic phase, an accelerated phase, and a blastic phase. More than 90% of CML patients have the Philadelphia chromosome abnormality (a shortened chromosome 22). A cytogenetic response, in which the Philadelphia chromosome is suppressed or disappears, seems to be a critical indicator of long-term disease control.

In 1986, Moshe Talpaz, M.D., of M. D. Anderson identified interferon-α as the first biological agent capable of producing a cytogenetic complete response in CML without destroying the bone marrow. This agent is now considered an important part of frontline therapy for most patients with chronic-phase CML. Furthermore, an early hematologic and cytogenetic response to initial interferon therapy is associated with better prognosis.

M. D. Anderson researchers are combining interferon with other agents in several clinical trials. One of these is low-dose cytarabine (also called *ara-C*), a cytotoxic agent that causes myelosuppression, which may add to the efficacy of interferon.

"In CML, we've established that interferon therapy combined with low-dose ara-C is improving the prognosis of patients," Dr. Kantarjian said. An initial trial of this combination in about 200 patients with chronic-phase CML resulted in a complete hematologic remission rate of 90% and a cytogenetic response rate of 70%, with tolerable side effects. The combination was more effective than interferon alone.

Dr. Talpaz, chairman ad interim of the Department of Bioimmunotherapy, and the leukemia research group are now studying combinations of a new agent, homoharringtonine (HHT), with interferon and ara-C for chronic-phase CML. In a study of 70 patients, HHT by itself induced complete hematologic remission in 72% and cytogenetic response in 30%.

"Patients respond very well, even if they are interferon resistant," Dr. Kantarjian said. Mild side effects, primarily diarrhea and headaches, were observed. Initial combination trials of HHT with ara-C or interferon also had encouraging response rates.

For patients whose chronic-phase CML has not responded after 12 months of interferon treatment and for those recently diagnosed who are young and have a matched sibling donor, the leukemia group generally recommends allogeneic stem cell transplantation if the mortality from the procedure is expected to be less than 20%.

For accelerated- and blastic-phase CML, researchers at M. D. Anderson are focusing on such new agents as decitabine, a hypomethylating agent. The aim is to combat the hypermethylation of DNA that is typical of disease progression.

"Our initial studies have had positive results, suggesting that decitabine does have activity," Dr. Kantarjian said. In 66 patients with advanced disease, 45% had a partial or complete hematologic response, and 5% had a cytogenetic response. The most common side effects noted were myelosuppression, febrile episodes, and infection, but these were acceptable, said Dr. Kantarjian. Future studies will combine decitabine with other active agents.

Because CLL originates in a different cell type, its behavior and the treatment strategies that are effective against it differ substantially from those of CML. The most effective agent so far is fludarabine, whose activity against CLL was established a decade ago by M. D. Anderson's Michael Keating, M.B., B.S., who is a professor of medicine in the Department of Leukemia.

Fludarabine, which interferes with DNA synthesis and repair, is now commonly given with cyclophosphamide, which induces DNA damage. This combination, which was pioneered by Susan O'Brien, M.D., of the Department of Leukemia, and William Plunkett, Ph.D., of the Department of Cellular and Molecular Pharmacology, has been tested in more than 200 patients, with response rates ranging from 85% in previously untreated patients to 30% in patients who have not responded to any other treatments. To deter infection in patients receiving this combination, Dr. O'Brien now uses granulocyte-macrophage colony–stimulating factor (GM-CSF) after chemotherapy. Her trial should determine if GM-CSF can speed bone marrow recovery by stimulating the differentiation of stem cells into new granulocytes and macrophages.

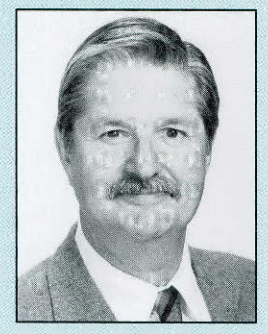
Another method of helping bone marrow recover from chemotherapy, called a "light" or "mini" transplant, is being employed by Issa Khouri, M.D., and Sergio Giralt, M.D., of the Department of Blood and Marrow Transplantation. Dr. Khouri, who combines a stem cell transplant with fludarabine and cyclophosphamide chemotherapy, said that the transplant may also have an antileukemic effect because the donated cells may recognize leukemic cells as

Researcher Matches Treatment Strategy to Genetic Mechanisms

For the researcher who more than a dozen years ago identified the oncoprotein Bcr-Abl produced by the Philadelphia chromosome, the cytogenetic hallmark of chronic myelogenous leukemia (CML), a major objective continues to be finding ways to treat the disease that the oncoprotein causes.

In 1985 Ralph Arlinghaus, Ph.D., now chairman of the Department of Molecular Pathology at The University of Texas M. D. Anderson Cancer Center, identified the oncoprotein encoded by the fused *abl* and *bcr* genes resulting from the translocation of chromosomes 9 and 22 evident in almost all CML cases. The Bcr-Abl oncoprotein causes CML, a leukemia characterized by an early benign phase (the chronic stage) and by subsequent evolution into a more aggressive malignancy.

> *"Our goal with the gene therapy treatment is to effect long-term responses in a larger proportion of patients at the early disease stage."*



Ralph Arlinghaus, Ph.D.
Chairman, Department of Molecular Pathology

The Philadelphia chromosome, the first genetic marker identified with a specific cancer, is found in 95% of patients with CML. But even in some of those patients with CML in whom the Philadelphia pattern is absent, Bcr-Abl fusion is detectable with molecular analysis. Cause of the breakage and translocation remains unknown.

Dr. Arlinghaus's gene therapy approach matches a unique strategy to the unique mechanisms of CML. Published findings from Dr. Arlinghaus's lab indicate that in healthy humans the Bcr and Abl proteins cross-inhibit each other, creating a well-regulated cellular environment. But when the Philadelphia chromosome abnormality occurs, these proteins become fused, and Abl takes the dominant role.

"We developed a mutant Bcr protein that can inhibit Abl but cannot be inhibited by Abl," explained Arlinghaus. "This mutant Bcr protein was built from the elements that allow Bcr to inhibit Abl. We hypothesize that when introduced into CML cells, the mutant Bcr protein will inactivate the Bcr-Abl oncoprotein and suppress the CML process."

Dr. Arlinghaus hopes that, based on this hypothesis, a new treatment can be developed to improve the survival and cure rates produced by chemotherapy with interferon and bone marrow transplantation, the leading treatment protocols for CML.

"Until the discovery of interferon as a therapy for CML," said Dr. Arlinghaus, "just about everyone who got CML died within three to four years of diagnosis." Currently, about 25% of patients who undergo interferon treatment experience a long-lasting response, and most others experience a temporary remission. About 15% of patients who receive bone marrow transplants from matched donors also have long-term remissions, which are cautiously identified as "cures."

"For reasons that are not well understood, a large subset of patients do not have long-term clinical remissions," said Arlinghaus. "We know that the best time to treat the disease is during the chronic stage. Our goal with the gene therapy treatment is to effect long-term responses in a larger proportion of patients at the early disease stage."

The mutant Bcr protein has not yet been tested in humans or animals. Only in vitro studies have been done so far, but the results have been very encouraging.

"We are fortunate in that we have been able to map the mechanisms that cause the disease," said Dr. Arlinghaus. "This information is crucial to treatment development. We know that CML is a disease that involves several molecular events as the patient progresses to a more aggressive leukemia. The first of these events is the fusion of the Bcr and Abl proteins. Later events involve additional genetic changes that are not well understood at this time. So, the sooner in the disease process we can introduce effective treatment, the better chance we have of altering the oncogenic process of CML."

–Vickie Williams

foreign and prevent recurrence.

For patients with CLL who do not respond to fludarabine treatment, two new second-line strategies are being tested. The first, CAMPATH-1H, is a monoclonal antibody that targets the CD52 antigen, which is expressed on the surface of many leukemic cells. Theoretically, by recognizing only cancerous cells, this antibody should reduce toxicity to healthy bone marrow and accompanying side effects. Patients may have fever, chills, and nausea, but hair loss and stomatitis have not occurred. Seven patients have received CAMPATH-1H so far at M. D. Anderson. "The three who can be evaluated have shown outstanding responses," Keating said.

The second new agent, compound 506, is a nucleoside analogue that seems to interfere with DNA synthesis and has shown activity in B- and T-cell CLL and T-cell acute leukemia. A phase I study has just been com-

(Continued on **page 4***)*

Trials for Chronic Leukemia Feature Chemotherapy and "Mini" Transplants

More than 30 clinical trials for patients with chronic leukemias are currently in progress at The University of Texas M. D. Anderson Cancer Center. These trials include some listed below. Contact the physician or visit the M. D. Anderson clinical trials listing on the World Wide Web (see numbers and addresses below) for more information.

- A phase II study of a nonablative preparative regimen with allogeneic blood progenitor cell transplantation for chronic myeloid leukemia (DM97-210). *Physician: Sergio Giralt, M.D.*

  In this trial, patients with chronic myelogenous leukemia (CML) will receive the drugs fludarabine, cytarabine, and idarubicin combined with a stem cell ("mini") transplant. Patients must have an HLA-identical sibling who is able to donate peripheral blood stem cells. Before collection of the cells, the donor will receive injections of granulocyte colony–stimulating factor (G-CSF) to boost the number of stem cells and granulocytes. Patients will receive the chemotherapy drugs intravenously starting six days before the transplant. Two days before the transplant, patients will begin receiving tacrolimus and methotrexate to prevent graft-versus-host disease. After the transplant, patients will receive G-CSF. Patients will need to stay at M. D. Anderson Cancer Center for about three weeks during treatment and in the Houston area for at least 100 days after treatment. Because low doses of the drugs will be used, older patients (up to 70 years) and medically infirm patients (Zubrod performance status of 2 or less) are eligible for this trial.

- A phase II study of high-dose intravenous busulfan and cyclophosphamide with allogeneic marrow or peripheral blood progenitor cell transplantation for hematologic malignancies (DM98-051). *Physician: Borje S. Andersson, M.D., Ph.D.*

  This trial, for patients with all phases of CML, is similar to the preceding one in that it combines chemotherapy with bone marrow rescue. The combination of busulfan and cyclophosphamide has been shown to have outstanding antileukemic activity. Busulfan has traditionally been given orally; in this trial, the drug is being given intravenously to reduce side effects of liver toxicity, nausea and vomiting, and nervous system toxicity. Included in the protocol are G-CSF, tacrolimus, and, in patients who have had central nervous system involvement, cytarabine and hydrocortisone to prevent damage to the nervous system. Stem cells or bone marrow will be transplanted from an HLA-identical donor who is related to the patient. Patients who are 13 to 60 years old and have a Zubrod performance status of less than 2 are eligible. After treatment, patients will need to stay in the Houston area three months or until platelet levels have stabilized, whichever is longer.

The following trials are described in the accompanying article.

- Therapy of chronic myelogenous leukemia with homoharringtonine and low-dose cytarabine (DM93-144). *Physician: Hagop Kantarjian, M.D.*
- Phase II study of simultaneous homoharringtonine and interferon-a therapy in chronic myelogenous leukemia (DM93-151). *Physician: Susan O'Brien, M.D.*
- Therapy of chronic myelogenous leukemia with interferon-alpha, low-dose cytarabine, and homoharringtonine (DM97-229). *Physician: Hagop Kantarjian, M.D.*
- Phase II study of decitabine in chronic myelogenous leukemia (DM 98-025). *Physician: Hagop Kantarjian, M.D.*
- Fludarabine, cyclophosphamide, and GM-CSF treatment of patients with chronic lymphocytic leukemia (DM96-316). *Physician: Susan O'Brien, M.D.*
- Phase I/II study of allogeneic peripheral blood stem cell infusion for patients with high-risk chronic lymphocytic leukemia (DM95-194). *Physician: Issa Khouri, M.D.*
- Phase II study of CAMPATH-1H in patients with B-cell chronic lymphocytic leukemia who have received an alkylating agent and failed fludarabine therapy (DM97-036). *Physician: Susan O'Brien, M.D., or Michael Keating, M.D.*
- A phase I study of 506U78 (compound 506) administered as a two-hour infusion on a day 1, 3, and 5 schedule in patients with refractory hematologic malignancies (DM96-312). *Physician: Michael Keating, M.D.*

FOR MORE INFORMATION *about these clinical trials, physicians or patients should contact the physician. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org.*

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pleted at M. D. Anderson, and a dose has been established for a phase II trial. Keating thinks combining compound 506 with fludarabine is promising as well.

For some of these agents, it is too soon to know whether the responses in these early studies will translate into longer patient survival; however, the proven activity of interferon and fludarabine have encouraged M. D. Anderson physicians to pursue new approaches. "We are now starting to study whether we can change the natural history of these diseases, with a view to curing them," Dr. Keating said. •

FOR MORE INFORMATION, *contact Dr. Kantarjian at (713) 792-7026 or Dr. Keating at (713) 745-2376, or call the M. D. Anderson Information Line at (800) 392-1611 or (713) 792-6161.*

HOUSE•CALL

Answering the Who, What, When, Why, and How of Cancer

Chances are, you already know someone who has cancer: a family member, a friend, or a co-worker. But how much do you know about cancer? Below are some basic facts and some pointers about finding more information.

What Is Cancer?

Cancer is not a single disease but many diseases. There are over one hundred different types of cancer. Cancer occurs when one or more cells in the body undergo a change in their genetic structure and begin multiplying in an abnormal way. These abnormal cells may form a tumor, which is a mass of excess cells. Tumors may be benign—no threat to life—or malignant—life-threatening. A malignant, or cancerous, tumor may eventually metastasize, or spread, to other parts of the body. Eventually, the abnormal cells can crowd out normal cells and affect normal body functions, causing illness. If this spread is not controlled, death may occur.

Cancer can appear in virtually any part of the body. Common sites are the skin, prostate, breast, lung, colon, pancreas, bladder, ovary, and lymph glands.

Why Does Cancer Occur?

Cancer has various causes, not all of which are known or understood. But two factors—diet and tobacco use—are believed responsible for most cancers. Other risk factors include exposure to certain chemicals (for example, benzene, asbestos, and arsenic) or to excess radiation (including too much sunlight). Some substances can promote cancer, that is, these substances alone do not cause cancer, but they are associated with cancer development. Alcohol, for example, is a cancer promoter.

An individual's genetic make-up also plays a role in cancer development. Some people (a minority) inherit a very strong tendency to develop cancer. Although genes that directly cause a person to have cancer are uncommon, certain genetic characteristics can combine with environmental factors to increase the likelihood of cancer. For example, fair-skinned people are more likely to sunburn and, therefore, have an increased risk of skin cancer. Black men are more likely to develop prostate cancer than are other men.

Human cancer is not contagious. You cannot "catch" cancer from someone else.

Who Gets Cancer?

Cancer occurs about equally in men and women. In the United States, over two million new cases of cancer are diagnosed each year, and cancer is the second leading cause of death (heart disease is first).

When Do People Get Cancer?

Cancer primarily affects people who are middle-aged or older, but cancer can occur in anyone at any age, from infants on up.

How Is Cancer Treated?

Standard cancer treatments include surgery, radiation therapy, chemotherapy, and hormone treatment (and often combinations of these). Newer therapies include genetic interventions, vaccines, and biochemotherapy. The treatment chosen depends on the type of cancer and the patient's condition. At M. D. Anderson Cancer Center, care is often administered in multidisciplinary centers where a variety of experts can provide reputable consultation.

If you need treatment for cancer, seek help and advice from knowledgeable sources. Some outright frauds and quacks prey upon people with cancer, giving false hope and no medical benefit.

Who Survives Cancer?

Many people successfully combat cancer. About half of all people who have cancer will survive. For some cancers, survival rates are very high; for others, they are low. Although different kinds of cancer have different survival rates, people have fought and survived every kind of cancer. For many cancers, the rates of successful treatment are now greater than ever.

How Do I Learn More?

To learn more about cancer, ask your doctor or talk to an oncologist (cancer specialist).

The Cancer Information Service (CIS) of the National Cancer Institute (NCI) provides up-to-date cancer information and can answer questions (in both English and Spanish) in nontechnical language. To reach CIS, call 1-800-4-CANCER (1-800-422-6237). Or visit the CIS Web site—http://rex.nci.nih.gov. Go to http://cancernet.nci.nih.gov to access the NCI's cancer research database, which includes information on new and experimental therapies. To contact the American Cancer Society (ACS), visit the ACS Web site at http://www.cancer.org. or call 1-800-ACS-2345 (1-800-227-2345). The M. D. Anderson Cancer Center also posts valuable information. Visit it at http://www.mdanderson.org.

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611 *within the United States, or*

(713) 792-6161 *outside the United States.*

June 1998

Ultrasonography Fosters Targeted Intraprostatic Therapy

by Sunita Patterson

Because the development of transrectal ultrasonography has made possible the precise delivery of agents to specific areas of the prostate, physicians at The University of Texas M. D. Anderson Cancer Center are now able to test two new intraprostatic therapies they hope will prove more effective and better tolerated than standard therapies.

Transrectal ultrasonography enables physicians to visualize the shape and volume of the prostate, choose the optimal target site, and guide the placement of needles through the perineum to it. This and other recent research advances are being exploited in protocols testing a brand new idea, gene therapy, and a new application of an old idea, brachytherapy.

"I feel like the flight pilot who gets to road test the Stealth bomber," said Louis Pisters, M.D., assistant professor in the Department of Urology. He and Christopher Logothetis, M.D., chairman of the Department of Genitourinary Oncology, are one of the first teams in the country to try intraprostatic gene therapy for prostate cancer. Dr. Logothetis is chairing the study.

"This trial is the result of a series of very rapid developments just in the last decade," Dr. Pisters said. Studies at M. D. Anderson Cancer Center and elsewhere have shown that mutations of the tumor suppressor gene *p53* are involved in the progression of a significant number of prostate cancers. The goal of *p53* gene therapy is to introduce a normal *p53* gene into prostate cells whose gene is damaged.

Another major advance that has made gene therapy possible is the development of vectors for transporting genes into the prostate. "We are using the adenovirus, an everyday cold virus," Dr. Pisters said. The prostate is susceptible to adenoviral infection, so the virus has a natural mechanism for getting into prostate cells.

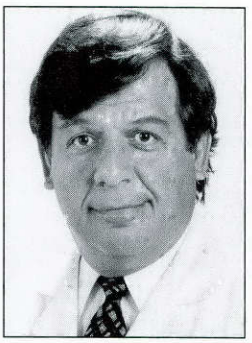
Drs. Logothetis and Pisters, as well as Curtis Pettaway, M.D., of the Department of Urology, are testing the gene therapy in patients who have locally advanced disease but no clinical evidence of metastasis. Specifically, patients have either clinical evidence of extracapsular extension (stage T2c), a high-grade tumor (Gleason score 8), or a high prostate specific antigen (PSA) level

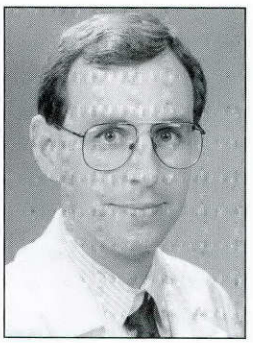
Pinpoints on screen represent brachytherapy seeds.

Radiation oncologist **Dr. Alan Pollack** *evaluates transrectal ultrasonographs in the dosimetry laboratory. Ultrasonography provides an accurate map of the prostate, and with it Dr. Pollack creates a computerized dosimetry plan. The computer application promotes optimal dose distribution in three dimensions to ensure therapy is uniform and adequate.*

"New technologies and ...knowledge...are increasing the probability that we're going to be able to control this disease more effectively."

– Christopher Logothetis, M.D.
Chairman, Department of Genitourinary Oncology





"This trial is the result of a series of very rapid developments just in the last decade."

– Louis Pisters, M.D.
Assistant Professor, Department of Urology

(>10 ng/ml). For these patients, the cure rate with standard therapy—surgery or radiation—is low (<30%).

Transrectal ultrasonography is used to guide the transperineal injection of the vectors into the prostate. Patients receive three separate injections of *p53* at two-week intervals. Afterward, physicians measure tumor size using ultrasonography and magnetic resonance imaging to evaluate effect. If the tumor is not shrinking, the patient is immediately scheduled for radical prostatectomy. If the tumor is shrinking, a second course of three injections is given before radical prostatectomy. Prostatectomy is part of the protocol to provide a backup inasmuch as the success of the gene therapy strategy has not yet been established. The prostatectomy specimen allows researchers to study the gene therapy's biologic impact.

Eleven patients have received the treatment at M. D. Anderson. "The efficacy should be known within a year," Dr. Logothetis said. "Thus far we can attest to the safety of the approach."

The gene therapy protocol is one of several at M. D. Anderson that are combining a preoperative therapy with prostatectomy. "We're trying to control the cancer before the surgery," Dr. Logothetis said. The goal is to prevent dissemination of microscopic deposits of tumor that might be missed by prostatectomy. Furthermore, Dr. Logothetis hopes that the preoperative therapy will work so well that prostatectomy will be unnecessary. In addition to using *p53* gene therapy as the preoperative regimen, Dr. Logothetis and his colleagues are also testing an angiogenesis inhibitor and a chemotherapy regimen (ketoconazole, doxorubicin, vinblastine, and estramustine).

Colleague Alan Pollack, M.D., Ph.D., associate professor of radiation oncology in the Department of Radiation Oncology, is also using an intraprostatic treatment technique—brachytherapy using transrectal ultrasonography planning and guidance. Selected patients undergo a single outpatient procedure for placement of radioactive seeds rather than the current external-beam radiation regimen of five exposures a week for seven to eight weeks.

When brachytherapy was tried in the past, the seeds were inserted blindly, under digital guidance. "There were probably significant problems with dosimetry," said Dr. Pisters, who is collaborating with Dr. Pollack on the new study. "Today, with transrectal ultrasound, we can plan in three dimensions how many seeds are needed and their ideal position, so that the dose distribution is uniform," Dr. Pollack said.

A planning ultrasonograph provides a map of the prostate, which is used to create a computerized dosimetry plan. As in the gene therapy protocol, transrectal ultrasonography is used to visualize the transperineal insertion of needles into the prostate. Through the needles, rows of seeds are deposited at intervals along predetermined coordinates. The seeds are permanent implants containing iodine 125 or palladium 103. Typically 70 to 100 seeds are used per patient.

In contrast to the gene therapy protocol, the patients who are candidates for the brachytherapy protocol have early (T2a), low-grade (Gleason score 6) prostate cancer. PSA level must be below 10 ng/ml, and a prostate volume of 40 ml is desirable. Hormone ablation can
be used to shrink the prostate before brachytherapy. Because there is a rapid falloff of dose with distance from the seeds, this modality is not appropriate for disease that extends beyond the prostate capsule.

"These are highly selected patients who have an excellent prognosis," Dr. Pollack said. In such patients, brachytherapy appears to be as effective as surgery or external-beam radiation therapy.

A typical side effect is urinary obstructive symptoms that may last several months, but medication is usually prescribed as a preventive measure. Also seen are transient irritative voiding symptoms. Serious complications leading to colostomy and urinary diversion are rare.

The brachytherapy and gene therapy trials have in common their direct therapeutic targeting of the prostate, their exploitation of transrectal ultrasonography to target the therapy, and their multidisciplinary origin.

"The availability of new technologies and the knowledge of the biology of prostate cancer that has been emerging in the last decade are increasing the probability that we're going to be able to control this disease more effectively," Dr. Logothetis said. ●

FOR MORE INFORMATION, *contact Dr. Logothetis at (713) 792-2830, Dr. Pollack at (713) 792-0781, or Dr. Pisters at (713) 792-3250.*

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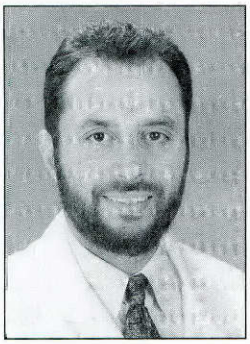
Leukemia's Lessons in Malignant Transformation

Hagop Kantarjian, M.D.
Professor of Medicine
Department of Leukemia



Leukemia is in some ways a case study for all malignant transformation. After all, it was in leukemia that a genetic rearrangement was first linked to cancer. With time, other researchers took the work further. Genetic understanding now drives our therapies.

Study of leukemia has been historic in other ways, too. In work done here at M. D. Anderson, researchers first used immunotherapy, with interferon, to prolong survival by suppressing neoplastic replication. Leukemia also provided the first model of differentiation therapy for cancer.

Treatment for leukemia most often is chemotherapy. Physicians have found more than 30 drugs that can combat leukemia alone or in combination. Supportive therapy makes it possible for patients to benefit from protocols whose side effects are otherwise too debilitating. Bone marrow transplantation, including "mini" transplantation, and immunotherapy are now being paired with new drugs that are creating remissions in patients whose disease has not responded to other therapies. Making bone marrow transplantation an option for more patients continues to propel the efforts of many.

Clinicians and researchers continue to move ahead. Just as researchers 30 years ago refused to accept a 4% survival rate, so today they are unwilling to be satisfied with the gains, though they are dramatic.

Undeterred by not knowing the causes of many leukemias, we are making therapeutic choices based on what my former colleague Kenneth McCredie, M.D., called "the biologic logic that underlies leukemia." Only now it is the molecular logic we are relying on, which we first glimpsed in chronic myelogenous leukemia and the Philadelphia chromosome. Using the broadening knowledge of cytogenetics in all leukemias, we can manipulate intracellular reactions and cell maturation with chemotherapy and other therapies to achieve apoptosis and to effect remissions.

In these ways leukemia research remains a unique opportunity to examine not only a microcosm of similar diseases but also the macrocosm of malignant transformation. As we take apart the complex puzzles of cellular phenomena and learn the intricacies of interacting mechanisms that rule cell growth and differentiation, we can hope eventually to unravel why certain people get the disease, how to identify them early, and how to prevent that series of molecular events known as leukemia. And as we gain this knowledge, we can hope that as in other advances in leukemia, its effect will be exponential and lead to progress against other neoplastic diseases.

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