Study of Epigenetic Changes Leads to Treatment Advances in Adult Leukemias

by Katie Prout Matias

As researchers in the exciting new field of study called epigenetics have found, genetic alterations are not the only genomic abnormality to play a major role in the development of cancer. Modifications in gene expression may be just as important as changes in gene structure when it comes to promoting cancer formation.

Most of these epigenetic changes arise spontaneously as a function of age and predispose cells to cancer transformation, according to Jean-Pierre Issa, M.D., an associate professor in the Department of Leukemia at The University of Texas M.D. Anderson Cancer Center. Environmental factors such as exposure to carcinogens, viral infections, and diet may also play a role.

"Leukemias have more epigenetic changes than other malignancies, followed closely by colon cancer," said Dr. Issa. "It could be that epigenetic information is particularly important in leukemias."

Understanding the mechanisms of epigenetic change

By identifying and targeting the two main mechanisms of abnormal gene expression—

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DNA methylation and histone modification—researchers are finding new ways to treat adult patients with leukemia.

DNA methylation, the addition of a methyl group to one of the bases of DNA, is a fundamental part of gene expression. The abnormal addition, removal, or placement of these groups, however, can lead to the loss of gene expression and to the activation or inactivation of important genes, such as tumor suppressor genes, DNA repair genes, and angiogenesis genes, said Dr. Issa. Abnormal DNA methylation occurs in most cancers.

The removal of acetyl groups, or histone deacetylation, allows the histones to bind to the DNA and keep it tightly wrapped so that cellular switches cannot access the genes to turn them on or off. “It is now thought that DNA methylation leads to histone changes and vice versa, so there is a loop that makes sure that the genes that are turned off by these mechanisms remain turned off,” said Dr. Issa. Without intervention, these changes in gene and protein expression are passed on to future generations of cells.

**Restoring normal gene expression**

Unlike genetic changes, however, epigenetic changes can be reversed. Researchers are investigating drugs that can inhibit histone deacetylation and strip DNA of the methyl group tags, thus restoring gene expression.

Investigators at M. D. Anderson are studying a new inhibitor of histone deacetylation called suberoylanilide hydroxamic acid (SAHA). When SAHA reverses histone deacetylation, the DNA unwraps from the histone core, allowing the genes to be activated. In the study, researchers are measuring histone changes before and after treatment in patients with acute myelogenous leukemia (AML).

In the area of DNA methylation, researchers are taking a second look at an older drug. Decitabine, which was developed in Czechoslovakia in the 1960s, is an analogue of cytosine that inhibits the methylation of certain genes. Hypomethylating drugs such as decitabine show promise for the treatment of leukemia, particularly when used in combination with other agents. In an upcoming clinical trial, researchers at M. D. Anderson will study the effects of decitabine combined with imatinib (Gleevec) in previously untreated patients with advanced (accelerated or blast phase) chronic myelogenous leukemia (CML) and in patients with refractory or imatinib-resistant CML.

**Improving the outlook for patients with CML**

Although it does not affect genetic expression, imatinib—a new and, so far, highly successful drug—is a targeted treatment that specifically blocks the protein of the fusion BCR-ABL gene that causes and marks CML.

“The perfect drug for cancer is sort of like imatinib: a drug that would target and kill only the cancer cells and not give you any side effects,” said Jorge E. Cortes, M.D., an associate professor in the Department of Leukemia. “It has changed the treatment of CML.”

Imatinib often helps patients in whom interferon and other treatments have failed and produces a complete cytogenetic response in more than 60% of previously untreated patients, while causing very few adverse effects. However, no long-term data exist regarding the durability of this response. In some patients, especially those with advanced stages of CML, the cancer does not respond to imatinib, and in others, the disease stops responding and becomes resistant.

“Imatinib is very new, and the failures to imatinib are only now starting to appear,” said Dr. Cortes. “We need to look at other treatments for patients in whom imatinib fails. Those patients with advanced disease are the perfect candidates to start from the beginning with a combination treatment based on imatinib.”

**Using epigenetic patterns to predict treatments, outcomes**

While combination therapy using imatinib and decitabine could improve...
"It could be that epigenetic information is particularly important in leukemias."

— Jean-Pierre Issa, M.D., associate professor, Department of Leukemia

the treatment response rates for patients with CML even more, progress in the treatment of other leukemias has not been as great. "In many other leukemias, especially AML, the signaling pathways that turn these cells leukemic are probably much more complex," said Stefan Faderl, M.D., an assistant professor in the Department of Leukemia. "Imatinib is a rather specific tyrosine kinase inhibitor that works very well in BCR-ABL-positive CML, but AML has proved much more resistant to this type of approach. Inhibiting a single signaling pathway will most likely not be sufficient in AML."

For these other leukemias—including AML, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS)—epigenetics may offer hope, not in drug development but through disease profiling and classification. Because different leukemias have distinct epigenetic patterns that are correlated with outcome and response to therapy, physicians are already using certain combinations of methylated genes to determine prognosis and treatment for subsets of patients.

Guillermo Garcia-Manero, M.D., an assistant professor in the Department of Leukemia, is building a database of epigenetic changes in ALL. "What is fascinating about ALL is that it is a very heterogeneous group of disorders. Although we call it one name, it is probably multiple diseases. And they have varying prognoses," said Dr. Garcia-Manero.

A certain combination of genes in ALL, when epigenetically inactivated, seems to result in a very unfavorable outcome for patients. This is important because if these patients do not have the Philadelphia chromosome, which is associated with a very poor prognosis, they are treated as if they have the more curable form of ALL. In fact, they should receive the same aggressive treatment, such as early bone marrow transplantation, given to Philadelphia chromosome-positive patients. Dr. Garcia-Manero suggested that patients with this epigenetic abnormality also might benefit from hypomethylating agents or histone modifiers in combination with chemotherapy.

"If we are successful and can correlate and confirm some of these results, then this will evolve into developing risk-adaptive therapies to determine who's going to do what and treat them with therapy based on their molecular and epigenetic profiles," said Dr. Garcia-Manero.

**FOR MORE INFORMATION, contact Dr. Issa at (713) 745-2260, Dr. Cortes at (713) 794-5783, Dr. Faderl at (713) 745-4613, or Dr. Garcia-Manero at (713) 745-3428.**

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**PROTOCOLS**

Studies Examine Treatment of Leukemia

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for patients with chronic myelogenous leukemia.

- **Phase I study of tipifarnib (Zarnestra, R115777,USA30) and imatinib mesylate (Gleevec, STI571) in chronic-phase chronic myelogenous leukemia (CML) (ID02-169).**

  **Physician:** Jorge Cortes, M.D.

  To be eligible for this study, patients must be 16 years old or older with Philadelphia chromosome-- or BCR-ABL--positive CML that failed to respond to previous therapy with imatinib mesylate. A Zubrod performance status ≤ 2 is required, as are adequate hepatic and renal function and a white blood cell count ≤ 30 × 10^9/L. Women who are pregnant or nursing are not eligible.

- **Therapy of early chronic-phase chronic myelogenous leukemia (CML) with higher-dose imatinib mesylate (Gleevec, STI571), interferon-alpha (IFN-α), and low-dose cytarabine (Ara-C) (Id01-151).**

  **Physician:** Jorge Cortes, M.D.

Participants must be 15 years old or older with Philadelphia chromosome-- or BCR-ABL--positive early chronic-phase CML. Patients must have received no or minimal prior therapy, except for hydroxyurea. Both male and female participants must use effective birth control methods during treatment and for at least three months afterward.

- **Phase II study of high-dose imatinib mesylate (Gleevec, STI571) for the treatment of late chronic-phase chronic myelogenous leukemia (CML) (ID01-292).**

  **Physician:** Jorge Cortes, M.D.

  This study is for patients in whom treatment with interferon-alpha has failed, patients with late chronic-phase disease who have not received interferon-alpha, or patients who refuse to take interferon-alpha. Participants must be 15 years old or older with Philadelphia chromosome-- or BCR-ABL--positive early chronic-phase CML.

- **A phase I/II study of clofarabine (Clofarex) in combination with cytarabine (Ara-C) in adult patients with primary refractory acute myelogenous leukemia (AML) or acute (Continued on page 4)
Phases of Imatinib Mesylate Treatment

- Phase II study of imatinib mesylate (Gleevec, STI571) and decitabine in chronic myelogenous leukemia (CML) in accelerated and blast phases (DM02-205). Physician: Jean-Pierre Issa, M.D.

Participants must be at least 18 years old and have adequate organ function. Participants of child-bearing potential must use effective birth control methods during treatment and for at least three months afterwards. Exclusion criteria include previous treatment with clofarabine; active, uncontrolled systemic disease; symptomatic central nervous system involvement; and concurrent chemotherapy.

- A phase II, multicenter study of decitabine in blast-phase chronic myelogenous leukemia (CML) that is refractory to imatinib mesylate (Gleevec, STI571) (DM02-133). Physician: Jean-Pierre Issa, M.D.

To be eligible, patients must have Philadelphia chromosome–positive blast-phase CML that is resistant or refractory to imatinib mesylate or be imatinib mesylate intolerant.

- Phase II study of lonafarnib (SCH66336) and imatinib mesylate (Gleevec, STI571) in chronic myelogenous leukemia (CML) (ID02-221). Physician: Jorge Cortes, M.D.

To be eligible, patients must be older than 16 years old and have chronic-phase CML that has failed treatment with imatinib mesylate alone or have accelerated- or blast-phase CML with or without prior treatment with imatinib mesylate. The patient must have a Zubrod performance status of 2 or better with adequate liver and hepatic function.

- Randomized trial of early chronic-phase chronic myelogenous leukemia (CML) with high-dose imatinib mesylate (Gleevec, STI571) alone or in combination with pegylated interferon-alpha-2b (Peg-Intron) and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim, Leukine) (ID02-534). Physician: Jorge Cortes, M.D.

To be eligible, patients must have Philadelphia chromosome–positive CML in early chronic phase and have received no or minimal prior therapy (< 1 month of prior interferon-alpha, with or without cytarabine [Ara-C] and/or imatinib mesylate). They must have a performance status of 0-2 and adequate liver and renal function. Women who are pregnant or nursing are not eligible.

For more information about these clinical trials, physicians or patients may call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson clinical trials Web site at www.clinicaltrials.org for a broader listing of treatment research protocols.

The Cost of Dealing

Patients who place their hopes and lives in the hands of their physicians tend to forget that doctors, despite their abundant skills and talents, are only human. In fact, those who dedicate their lives to caring for the sick often do so at great personal cost. And nowhere is that price higher than in the field of oncology.

The psychological needs and burdens of patients with cancer and their families place a particularly heavy load on oncologists, according to Walter F. Baile, M.D., professor and chief of the Section of Psychiatry in the Department of Neuro-Oncology at The University of Texas M. D. Anderson Cancer Center. A 1991 study in the Journal of Clinical Oncology reported that 56% of medical oncologists, radiation oncologists, and surgeons who responded to a survey were experiencing burnout. The major reasons cited, according to Dr. Baile, were "the difficulty of dealing with patients who didn't get better and feeling frustrated that there weren't more treatments to effect a positive outcome for these patients."

Many cancer specialists find end-of-life care grueling, frustrating, and stressful. "It confronts them with issues of dying to which little attention has been given in their training," Dr. Baile said. "The average oncologist probably gives bad news 20,000 times during the course of a career, and there is very little preparation on how to do that well."

A study of British oncologists showed that 28% had psychiatric disorders, such as anxiety and depression, due to patient overload, concern about treatment toxicity, and low satisfaction with their work. Another study, this one of Canadian oncologists, found that 53% felt emotionally exhausted and rated their
level of personal accomplishment as low. Many were considering leaving the field of oncology.

Most physicians possess characteristics that help them provide excellent patient care but make them more likely to suffer from burnout, Dr. Baile said. These traits include working very long hours, denying their own needs, finding it difficult to ask for help, sacrificing their family and personal life for their jobs, taking a tremendous amount of responsibility for their patients, being very self-critical, and being unable to say "no" to requests for additional time and effort.

On the other hand, an important finding from the study of British oncologists was that doctors who had better interpersonal communication skills were less likely to experience burnout, Dr. Baile said. "Unfortunately, medical training often overemphasizes technical skills at the expense of interpersonal ones." Physicians with good communication and interpersonal skills receive more positive feedback from patients, which can be a buffer against burnout.

Acknowledging the emotional toll that their work exacts also can help oncologists deal with their stress, said Dr. Baile. But physicians sometimes have problems discussing the difficulties of their work. Part of this reluctance is due to "a principle in the culture of medicine not to talk about your feelings regarding patient care, overload, or burnout," Dr. Baile said. But reluctance to talk about problems can lead to irritability, burnout, and a cynical attitude toward medicine. If the problems persist, some physicians may turn to substance abuse or suffer sleep deprivation and exhaustion.

To help clinicians, as well as researchers, recognize and deal with workplace stress, M. D. Anderson formed a Faculty Health Committee, which is chaired by Ellen R. Gritz, Ph.D., professor and chair of the Department of Behavioral Science. Kathleen Sazama, M.D., J.D., then vice president for Faculty Academic Affairs at M. D. Anderson, provided administrative leadership. The committee's goal is to help faculty members recognize the signs of dangerous stress and be aware of the mental health resources available to them.

"We want faculty to be aware of what amount and type of stress is normal in the workplace and how to realize when stress has gone beyond their ability to manage it. And we want to let them know what solutions are available," said Dr. Sazama, now a professor in the Department of Laboratory Medicine.

To kick off the Faculty Health Committee's efforts, John-Henry Pifferling, Ph.D., and Louise Andrew, M.D., J.D., from the Center for Professional Well-Being in Durham, North Carolina, will present "Faculty Quality of Life: An Endangered Topic" on May 20.

Other resources for dealing with stress include counseling through M. D. Anderson's Employee Assistance Program and a proposed Faculty Assistance Program, a confidential service that will be staffed by outside mental health professionals.

Dr. Baile and Janis Apted, director of Faculty Development, also are designing a series of monthly seminars for M. D. Anderson clinicians on "Dealing with Difficult Situations." The seminars, which will begin in the fall of 2003, will show clips from the video "On Being an Oncologist: Reflections on the Personal Dimensions of Clinical Oncology" (see related article on page 6) to stimulate discussion and may include role-playing.

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The Cost of Caring

(Continued from page 5)

Dr. Ellen R. Gritz, professor and chair of the Department of Behavioral Science, chairs the Faculty Health Committee at M. D. Anderson.

exercises on topics such as how to deal with an angry patient, Apted said.

What else can oncologists do to minimize their stress? Dr. Baile described some wellness practices that physicians have reported as being helpful. First, he said, clinicians have to do some self-assessment. “Ask yourself how much you’re overcommitted to work at the price of other things in your life, how satisfying the job and work environment are, and how much you’re denying your own needs,” he said.

One of the most important wellness practices is “adopting an approach to life that’s based on a balance between work, home life, and relationships and friends, which can be great buffers against stress,” Dr. Baile said. Many physicians have made efforts to simplify their lives by shedding some responsibilities and focusing more on taking care of themselves. They may decide to exercise more, put more emphasis on spirituality, or start regular meditation. Attending a retreat that emphasizes self-reflection, the reestablishment of goals for the future, and renewal can also be extremely helpful. Many people, Dr. Baile said, go into medicine because of the value they place on patient care, healing, and helping others. It is beneficial for these physicians to have an opportunity to “reexamine what are the satisfying parts of practice in their lives and what aspects they’re dissatisfied with and work on change where that’s possible,” he said.

FOR MORE INFORMATION, contact Dr. Baile at (713) 792-7546, Dr. Sazama at (713) 792-7791, Dr. Gritz at (713) 745-3187, or Janis Apter at (713) 792-8061.

Excerpts from Focus Groups Featured in Video to Help Oncologists Cope with Stress

by Karen Stuyck

"On Being an Oncologist: Reflections on the Personal Dimensions of Clinical Oncology" is a video program and workbook designed to help promote discussion about the work of being an oncologist. Walter F. Baile, M.D., professor and chief of the Section of Psychiatry in the Department of Neuro-Oncology at The University of Texas M. D. Anderson Cancer Center, and Robert Buckman, M.D., Ph.D., a professor and medical oncologist at the University of Toronto, developed the program, which was introduced at the 2002 American Society of Clinical Oncology meeting.

The video evolved from a series of focus groups in which M. D. Anderson clinicians and clinical fellows discussed the rewards, demands, and emotional costs of being an oncologist. Excerpts from these discussions were used to create the text of the video, with actors Megan Cole and William Hurt playing the parts of two colleagues talking about such issues as handling time pressures, breaking bad news to patients, dealing with a patient’s death, and coping with stress. Cole, who starred as a woman dying of cancer in several productions of the play Wit, also helped lead the focus groups.

In the section on time pressures, for instance, Hurt tells Cole, “It’s four in the afternoon and I’m supposed to take my daughter to her soccer game, but I’m four hours behind and I’m not going to make it. And then I’m angry—with myself, the place, the schedule, and everybody else.”

Cole says, “It’s much more draining...having to spend a lot more time with these patients who are having trouble accepting that they’re dying. It’s psychologically draining. I feel guiltier, I feel worse that I can’t help them because they feel so bad. I feel that I’m not adequately treating the patient.”

In the section on coping, Hurt and Cole relate some of the ways that members of the focus groups deal with stress: having hobbies (“something not medicine-related”), taking time away from clinical duties (“time to rest from the experience...gives me emotional energy to be completely committed when I am on the floor”), talking to trusted colleagues (“When I say I screwed up, they give me an honest opinion”), and going on vacation (“You realize everyone in the world doesn’t always think about cancer”).

Cole, in her role as doctor, says, “I’ve come to realize that I’m struggling hard because it is hard. It’s not easy to know what to do. It’s not just black and white.”

The workbook for “On Being an Oncologist: Reflections on the Personal Dimensions of Clinical Oncology” includes eight sections, with topics for individual reflection or group discussions at the end of each section. Also included is a bibliography of relevant readings. Physicians can obtain three hours of continuing medical education credit by completing and submitting a test at the end of the workbook.

EDITOR’S NOTE:
Readers interested in receiving a free copy of the “On Being an Oncologist” video and accompanying workbook should e-mail Janis Apter at japter@mdanderson.org.
When most people think of cancer prevention, they envision such activities as stopping smoking, using sunscreen, and eating more fruits and vegetables. In addition to these precautions, however, another approach, called chemoprevention, is gaining ground. Chemoprevention, which is being tested in many different types of cancers, makes use of natural or synthetic substances to prevent cancer.

Researchers have identified about 400 drugs, vitamins, hormones, and other agents that may help prevent cancer, according to the National Cancer Institute (NCI). Clinical trials (research studies involving people) are under way to investigate more than 40 of these potential chemopreventive agents. These clinical trials, which usually involve healthy people who have a higher-than-average risk of cancer, compare the incidence of cancer in people who took the chemopreventive agent with the incidence in those who did not.

Scientists now see cancer as the result of a multistage disease process called carcinogenesis. Twenty years or more may pass from the start of the disease process, when the first cells begin to mutate, until the latter stages when the cancer is advanced. By using chemopreventive compounds during the early stages of carcinogenesis, researchers hope to stop the cancer from developing.

Preventing breast cancer in women at high risk

One of the first studies to show the effectiveness of a chemopreventive agent was the Breast Cancer Prevention Trial, which concluded in 1998. In the trial, healthy women at high risk of breast cancer were randomly divided into two groups. One group was given the chemoprevention drug tamoxifen, while the other group took a placebo. The group that took tamoxifen had 49% fewer cases of breast cancer than the placebo, or control, group. Tamoxifen interferes with the female hormone estrogen, which breast cancer cells need to grow and divide.

Currently, the Study of Tamoxifen and Raloxifene (STAR) trial is comparing tamoxifen with another drug, raloxifene, in hopes that raloxifene will be equally effective in preventing breast cancer but cause fewer adverse effects.

Both tamoxifen and raloxifene are selective estrogen-receptor modulators, one class of promising chemopreventive agents. Other compounds being studied in clinical trials to determine their ability to prevent cancer include nonsteroidal anti-inflammatory drugs (NSAIDs), calcium compounds, glucocorticoids (a type of steroid), and retinoids (derivatives of vitamin A).

Chemoprevention studies in other cancers

In addition to breast cancer, researchers are investigating the use of chemopreventive agents to prevent cancers of the colon, head and neck, prostate, esophagus, bladder, lung, cervix, and skin.

In the largest cancer prevention study ever conducted, researchers at M. D. Anderson Cancer Center and approximately 400 other institutions are recruiting more than 32,000 men to participate in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). This trial is investigating whether supplements of vitamin E and the dietary mineral selenium can help prevent prostate cancer.

In another M. D. Anderson study, a derivative of vitamin A, 13-cis-retinoic acid, was shown to be effective in preventing second primary tumors in patients who had been successfully treated for head and neck cancer. Several ongoing clinical trials concern the prevention of colon cancer. In some studies, people with a family history of colon polyps or cancer are taking NSAIDs, such as aspirin or celecoxib, in hopes of preventing colorectal cancer. People who have been previously diagnosed with colon polyps or cancer are participating in chemoprevention clinical trials that study calcium compounds as preventive agents.

Lowering cancer risk in the general population

While researchers so far have focused their chemopreventive studies on people at higher risk of cancer, long-term clinical trials with thousands of participants will be needed to determine whether a substance will lower the risk of cancer in the general population.

More information about current chemoprevention clinical trials is available by calling the Cancer Information Service (1-800-4-CANCER) or by visiting the clinical trials page of the NCI's Web site (http://cancer.gov/clinical_trials/) or M. D. Anderson's chemoprevention Web site (http://www.mdanderson.org/topics/chemoprev).

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 in Houston and outside the United States.

April 2003
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Below is a partial list of staff publications appearing this month.


Kumar R. Another tie that binds the MTA family to breast cancer. Cell 2003;113(2):142-3.
