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**REPORT TO
PHYSICIANS**

**DECEMBER 2000
VOL. 45, NO. 12**

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

3

Neutropenia

Prevention, treatment, and management strategies aim to control infections.

Compass

Quarterly Supplement

Clinical guidelines for the treatment of acute leukemia are featured.

5

Patient Education

House Call offers tips to help patients communicate with their doctors.

7

OncoLog Index-2000

Year-end index makes it easy to find topics, articles, and people featured in 2000.

MD Anderson OncoLog

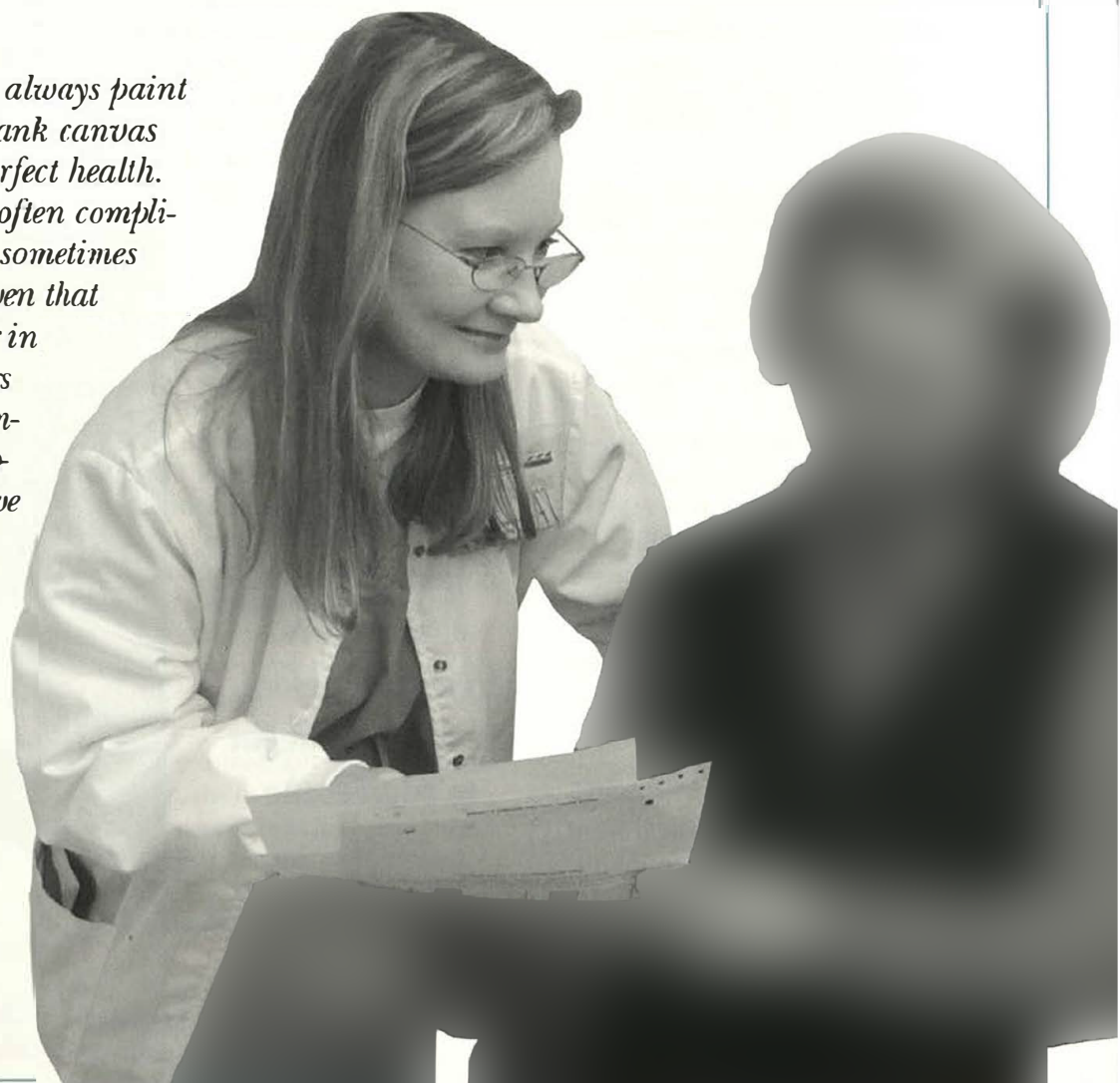
And Cancer Too: Treating Cancer Alongside Other Conditions

by Sunni Hosemann

Cancer does not always paint itself onto a blank canvas of otherwise perfect health. The picture is often complicated by other, sometimes chronic or severe, illnesses. Given that most new cases of cancer occur in people who are at least 50 years old, conditions such as hypertension, chronic obstructive pulmonary disease, diabetes, congestive heart failure, and coronary artery disease frequently predate the cancer diagnosis. If not managed appropriately before and during cancer treatment, these comorbid conditions could have devastating consequences.

(Continued on next page)

Kimberly Desrouleaux, R.N., goes over the results of coagulation studies with [REDACTED], who has diabetes and is receiving Coumadin for a deep vein thrombosis.



Treating Cancer Alongside Other Conditions

(Continued from page 1)

“We often see patients who have not seen a doctor for years but nevertheless have serious medical conditions, some that require treatment before we can even begin to address the cancer,” said Edward Rubenstein, M.D., a professor in the Section of Medical Supportive Care in the Department of Anesthesiology at The University of Texas M. D. Anderson Cancer Center.

Dr. Rubenstein recently treated a patient who had to undergo heart surgery to correct a long-standing aortic valve condition before he could begin cancer therapy.

“It was a very rough year for him, with two major medical events, but he is fully recovered from both now, can sustain an activity level he had not been able to achieve in years, and is quite amazed at how much better he feels. He just did not realize how severely compromised he had been by the cardiac problem,” said Dr. Rubenstein.

Of all comorbidities, cardiovascular conditions are most likely to need immediate medical attention before cancer treatment begins; however, many other conditions can affect a patient’s health and possibly influence the course of treatment for cancer.

For many cancers, surgery is the first intervention, and a patient’s ability to tolerate a procedure can be a critical factor in determining the course of treatment. Although some surgical techniques are quite advanced, they may nevertheless be quite aggressive. Internal medicine specialists at M. D. Anderson perform perioperative assessments of patients with comorbidities to determine their ability to tolerate surgery. For example, pulmonary function and reserve are critical determinants of the feasibility and limitations of lung resection.

Comorbidity is also an important factor in nonsurgical cancer treatments. Certain chemotherapeutic agents are toxic to specific organs—

cisplatin to renal tissue, anthracyclines to cardiac tissue, and other agents to lung tissue—so underlying conditions may well affect the choice of drug therapy, and in some cases, chemotherapy may be contraindicated. In addition, radiation oncologists are very concerned about the effects of radiation on patients with tissue disorders like scleroderma or other collagen-elastin diseases.

When Mary Ann Weiser, M.D., Ph.D., an assistant professor in the Department of General Internal Medicine, treats patients with comorbid conditions, she routinely consults with her colleagues in both radiation oncology and medical oncology during the patient’s chemotherapy and radiation treatments.

“We see many patients who are diabetic or who have hypertension, coronary artery disease, or other cardiac conditions,” Dr. Weiser said.

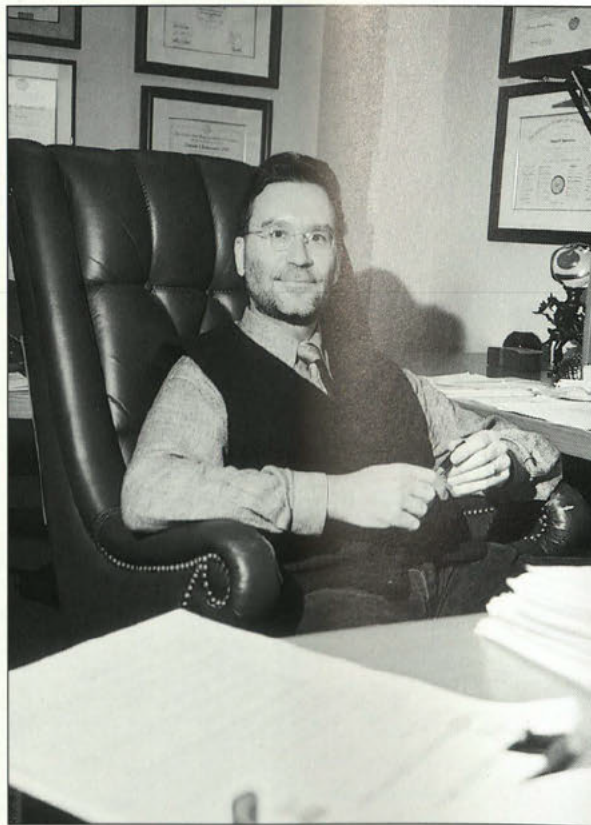
Even if these conditions are under

control, they become part of the picture, as do the medications used to manage them, which may interact with agents used in cancer chemotherapy. For example, patients taking Coumadin (warfarin sodium) for atrial fibrillation, deep vein thrombosis, prosthetic valves, or previous pulmonary emboli must be carefully monitored, as certain antineoplastic regimens, as well as some antibiotics and antifungal agents, change the way Coumadin is metabolized. It is also sometimes necessary to change the titration levels of Coumadin, depending on the bleeding risks associated with the patient’s cancer.

Patients with diabetes always require extra vigilance and frequent monitoring of blood glucose levels, not only during surgical procedures but also during the entire course of cancer treatment. Steroids, which are part of some chemotherapy regimens, tend to provoke episodes

“We often see patients who have not seen a doctor for years but nevertheless have serious medical conditions, some that require treatment before we can even begin to address the cancer.”

— Edward Rubenstein, M.D., professor, Section of Medical Supportive Care



of hyperglycemia. In fact, said Dr. Weiser, these agents occasionally unmask diabetes or precipitate its onset in patients who were not previously diabetic.

Changes in food intake are also common in the setting of cancer care. Sometimes, these changes are caused by the cancer itself, but they can also be associated with chemotherapy and radiation treatments. For patients with diabetes, for example, nausea, vomiting, and loss of appetite may affect blood sugar control, as may mucositis, which develops in some patients undergoing radiotherapy and can also occur in patients receiving some forms of chemotherapy. Occasionally, dietary changes are more dramatic, as in patients who must receive tube feedings or who have had their normal diets replaced by parenteral nutrition during their illness.

As one might expect, patients with hypertension also require extra surveillance during cancer treatment. Sometimes this involves a change in medication or a temporary change in the route of administration, such as when it becomes difficult or impossible for patients to take their pills orally. Sometimes a patient's clinical picture will change as a result of the cancer or its treatment. Weight loss, for instance, may actually improve the control of hypertension and diabetes.

Kimberly Desrouleaux, R.N., a clinical nurse in the Department of Internal Medicine Specialties, works on the front lines, assisting patients with cancer who have coexisting medical conditions. Her major responsibilities include monitoring her patients' blood sugar, prothrombin time and international normalized ratio levels (for patients taking Coumadin), and blood pressure. Desrouleaux experiences firsthand the challenges of internal medicine practice, in which meticulous and vigilant monitoring and titration of medications are necessary to achieve

"I find that many people who are affected by cancer are very motivated not only to participate in their cancer care but also to keep their other conditions in control."

— Kimberly Desrouleaux, R.N., clinical nurse, Department of Internal Medicine Specialties

disease control in a complex setting. She sees and talks with her patients frequently and, as nurses often do, has developed special insights into their care. Many patients, she said, come from settings where health has not been a priority for them or their families.

"So we do see noncompliance, whether because of depression, lack of education, background, or all of these factors. And these are situations that represent a huge challenge," said Desrouleaux. But there are also significant rewards, she added. "I find that many people who are affected by cancer are very motivated not only to participate in their cancer care but also to keep their other conditions in control. For many patients, this gives them some control and thereby eases some of their stress. And they are often very grateful for the extra surveillance and frequent contact." ●

FOR MORE INFORMATION, contact Dr. Rubenstein at (713) 794-4319 or Dr. Weiser at (713) 792-4589.

Controlling Infections in Patients with Neutropenia Remains a Challenge

by Noelle Heinze

Because cancer cells are so adept at insinuating themselves within the body, cancer therapies often walk a fine line between healing and harm. The same treatments used to save the lives of patients with cancer can also damage their immune systems, and the most common manifestation of this damage is neutropenia.

A condition characterized by a neutrophil count below 1,000/mm³, neutropenia puts patients at risk for infection by a multitude of organisms, as well as other serious complications. Although neutropenia will exist as long as myelosuppressive therapies exist, the number and severity of its associated infections can be minimized by careful prevention, treatment, and management.

Prophylactic antibiotics, various isolation techniques, and protected environments are often used to prevent infections in patients at high risk or to prevent existing infections from spreading to others. However, despite preventive practices, a severely weakened immune system is an invitation for infection, and diagnosing an infection can be just as challenging as preventing one in patients with neutropenia.

"It is difficult to determine an

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Controlling Infection in Patients with Neutropenia

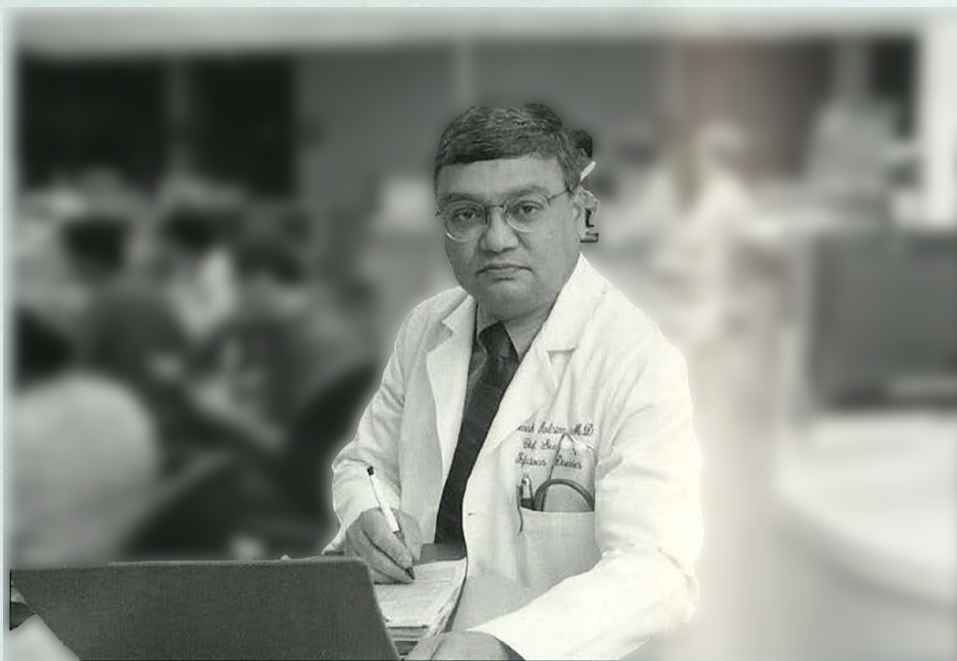
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infection in these patients because their immunity is low and their inflammatory response is blunted, so they don't often give you the same signs and symptoms as an immune-competent person does," said Kenneth Rolston, M.D., professor and chief of the Section of Infectious Diseases in the Department of Internal Medicine Specialties at The University of Texas M. D. Anderson Cancer Center. Fever or shortness of breath may be the patient's only symptom, Dr. Rolston said, so the tools for making a specific diagnosis are not always available.

Blood and urine cultures, biopsies of visible lesions, and imaging techniques such as chest x-rays, computed tomography, and magnetic resonance imaging can help identify some infections, and newer techniques that use polymerase chain reaction analysis and measure antigens or antibodies for specific pathogens are also being evaluated. However, a specific diagnosis is not made in 40% to 60% of patients with neutropenia. In these cases, the patients are still treated with antibiotics because of the high probability that an infection exists.

"Infections in patients who are neutropenic can develop very quickly, and they can disseminate or progress very quickly," explained Dr. Rolston. "So although the standard way of managing infections in patients who are not immunocompromised is to make a specific diagnosis and then treat, you cannot wait for a specific diagnosis to treat patients with neutropenia," he said. At M. D. Anderson, patients with febrile neutropenia undergo a diagnostic workup quickly, and treatment is started based on which infectious organisms are anticipated to be present.

Many different antibiotic, antifungal, and antiviral protocols or specific drugs are available, depending on a patient's susceptibility to certain infections. Dr. Rolston emphasized that different patients qualify for



According to Kenneth Rolston, M.D., professor and chief of the Section of Infectious Diseases, infections in patients with neutropenia tend to develop and spread quickly, so treatment is often begun before a specific diagnosis is made.

different treatment options and that all of these options should be used within a single institution rather than using the same drugs or regimens to treat everyone.

"This way, bugs encounter different defenses, and they don't become resistant to any one particular option," he said. Among the many antibacterial regimens used for the treatment of infections at M. D. Anderson are aminoglycosides plus β -lactam, vancomycin plus β -lactam, quinolones (which are also used for prophylaxis), and broad-spectrum penicillins. In addition to antibiotics, growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor are sometimes given to boost a patient's immune system, as are white blood cell transfusions and immune globulins.

Researchers in the Department of Health Services Research and in the sections of Infectious Diseases, Infection Control, and General Internal Medicine within the Department of Internal Medicine Specialties have focused on the problem

of neutropenia and made important contributions to current clinical practice guidelines.

At M. D. Anderson, patients at low risk are treated in the outpatient setting with oral rather than intravenous antibiotics when appropriate. "More than 90% of patients respond in the outpatient setting, and the 10% who don't respond have a prolonged fever but don't get into trouble with septic shock, intensive care unit admissions, or major complications," said Dr. Rolston.

Technological advances may make prevention and treatment of infections easier, and the infections may become more responsive, but Dr. Rolston does not anticipate that the problem will go away.

"I see it changing," he said. "I see the playing field changing, but the key is going to be to try to develop techniques and strategies that produce antitumor responses without causing such destruction of the immune system." ●

FOR MORE INFORMATION, contact Dr. Rolston at (713) 792-6830.



How to Talk with Your Doctor

Advances in cancer treatments and the explosion of cancer research and clinical trials in the past few years mean more treatments are available for patients with cancer. Often, patients are faced with several treatment options that could lead to the same outcome but have different limitations and side effects. So how do you know which treatment is right for you? With the help of your doctor and the support of family and friends, you can gain a better understanding of your disease and make informed decisions about your treatment.

Communication involves not only understanding what your doctor tells you but also making your needs and wants clear to your doctor. Below are some tips for talking with your doctor that will help you leave his or her office informed of your options and able to make important decisions.

Before your appointment:

- Decide what type of doctor-patient relationship you want. Do you want your doctor to describe your options and leave the decisions to you, offer suggestions for the treatment plan, or make the decisions for you? Be sure to let your doctor know which kind of relationship you prefer so he or she can act accordingly.

- If you decide that you want to make some or all of the decisions regarding your treatment, you will need to be prepared. Do as much research as possible through sources such as medical journals, Internet sites, and your telephone. Good online sources of information are the American Cancer Society (www.cancer.org), the National Cancer Institute (www.cancer.gov), and the Cancer Information Service (CIS) (cis.nci.nih.gov). CIS also has a toll-free telephone number (1-800-4-CANCER).

- Write all the questions that you have on a notepad, and take it with you to your appointment. Be sure to ask all of your questions, and don't

be embarrassed about writing down your doctor's answers. Doctors appreciate a patient's desire for knowledge and communication. Here are some questions you might consider asking:

- ✓ *What is my diagnosis?*
- ✓ *What are my treatment options?*
- ✓ *What are some likely side effects of the treatment?*
- ✓ *Will I be able to carry on normal activities during treatment?*
- ✓ *Will I be hospitalized during the course of my treatment?*

- Although you will probably see several doctors during the course of your cancer treatment, it may be helpful to choose one doctor as your primary source of information and establish a level of trust with that doctor. This will allow you to feel secure in the recommendations of your doctor and in your treatment plan.

At your appointment:

- Bring a friend or family member to the appointment with you for

moral support and to help you ask questions and remember important information.

- If you don't understand something your doctor tells you, keep asking questions until you do. Understanding your options is vital to helping you make decisions that are right for you.

- Tape record the visit so that you can listen again at home. This way, you can replay the doctor's words as often as you want to increase your level of understanding. Just be sure to ask the doctor's permission to record first.

- Before your appointment ends, make sure you know what the next step in your treatment plan is. Will you need to set up another appointment? Arrange for tests at another location? Make an appointment with another doctor?

After your appointment:

- Based on what your doctor told you during your appointment, you may want to conduct more research on the particulars of your treatment options when you get home.

- What if you think of one more question after you arrive home from your appointment? Before leaving your doctor's office, find out how he or she prefers to communicate—perhaps by telephone or e-mail. ●

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.

December 2000

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New Study Measures the Effects of Mood and Hereditary Tendencies to Smoke on Tobacco Cessation

by Alison Ruffin

It's 11 a.m., and [REDACTED] a smoker, has not had a cigarette for 12 hours. In his nicotine-deprived state, [REDACTED] steps into the Tobacco Research and Treatment Laboratory at The University of Texas M. D. Anderson Cancer Center and sits quietly as a research assistant attaches electrodes to his head and hands to record his responses to a series of photographs. Afterwards, the level of carbon monoxide in [REDACTED] lungs is measured, and he answers questions about his mood, anxiety level, and family history.

What researchers hope to discover with the help of [REDACTED] and other volunteers is how smoking and nicotine withdrawal affect mood in smokers, including those who may have inherited a susceptibility to nicotine addiction. The National Cancer Institute is funding the two-year, \$260,000 study entitled "Psychophysiological Examination of the Emotional Responses of Smokers," or PEERS.

Like many people who are addicted to nicotine, [REDACTED] comes from a family of smokers, a fact that may indicate a hereditary predisposition to smoking, according to researchers.

"Understanding the relationship between genetic factors affecting mood and the effects of nicotine on mood may ultimately help us develop more effective tobacco cessation programs," said Paul M. Cinciripini, Ph.D., director of the Tobacco Research and Treatment

Tobacco Use and Health

- Tobacco use is the predominant risk factor for the development of lung cancer. Other risk factors include exposure to carcinogenic substances such as secondhand smoke, arsenic, radon, and asbestos.
- Tobacco is responsible for more deaths per year in the United States than alcohol, heroin, cocaine, suicide, homicide, car accidents, fire, and AIDS combined.
- Tobacco-related medical costs in the United States total more than \$100 billion per year.

Quitting Smoking

- Reduces the risk of cancers of the lung, head and neck, bladder, colon, rectum, pancreas, and cervix
- Improves wound healing
- Reduces complications after surgery
- Improves circulation and reduces the risk of heart disease
- Improves breathing and lung capacity
- Reduces health care costs

Program at M. D. Anderson and principal investigator of the study.

Previous research has shown that some smokers receive more pleasure from nicotine than others because of changes in the level of the brain chemical dopamine, a finding that suggests a possible hereditary component to nicotine addiction. For this reason, some smokers are able to

quit "cold turkey," and others have a more difficult time quitting.

PEERS researchers are measuring exactly how nicotine withdrawal affects mood in smokers with and without a hereditary susceptibility to smoking.

Smokers who volunteer for the study view pleasurable, aversive, and smoking-related pictures—including images of burn victims and sexual images—in a nicotine-deprived state while their physical responses to each are measured.

"We record participants' physiologic responses to the pictures, including eye-blinks, frowns, smiles, and palm perspiration," said Dr. Cinciripini.

Enrollment in the study is open to smokers from 18 to 59 years old who smoke 10 or more cigarettes per day. Participants come to M. D. Anderson for five two-hour laboratory sessions.

Other tobacco cessation studies at M. D. Anderson currently enrolling volunteers include:

— A study of computer-assisted smoking cessation that combines several smoking cessation techniques (scheduled smoking, nicotine patches, and the use of a hand-held computer) to learn which combination of treatments is most effective.

— A smoking cessation study for community college students that helps young smokers better understand their level of nicotine dependence, heightens their awareness of the dangers of tobacco use, and enables them to plan the most effective method to quit smoking.

— A study to test the effectiveness of a new treatment program, Project STOP, which includes use of a nicotine patch, self-help materials, and counseling to help smokers quit and stay off cigarettes forever. ●

FOR MORE INFORMATION, call (713) 792-2265 or visit the cancer prevention Web site at www.mdanderson.org/prevention.

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Staff Publications in December

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

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This guideline may assist in the diagnostic evaluation of patients with clinical symptoms or positive screening tests (if such testing exists). The clinician is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care.

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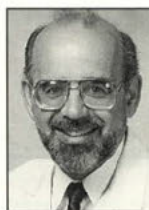
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An expanded version of these materials with CME category 1 credit is available on the Internet. Access Practice Guidelines from M. D. Anderson's Home Page at <http://www.mdanderson.org>.

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CLINICAL DISCUSSION: Acute Leukemia

Scope of This Guideline

This guideline addresses the evaluation, treatment, and follow-up care of adult patients with acute myelogenous leukemia (AML), including acute promyelocytic leukemia (APL) and myelodysplastic syndrome (MDS). Adult chronic leukemias, acute lymphocytic leukemia (ALL), and the childhood leukemias are biologically and clinically different than AML, APL, and MDS and require different management approaches. They are not addressed here.

Synopsis & Highlights

Overview

The leukemias are a group of cancers characterized by the infiltration of bone marrow by abnormal cells that arrest the maturation of cells at an early phase of hematopoietic differentiation. AML is an acute-onset disease that is usually fatal within six to 12 months of diagnosis. Previously, AML was distinguished from myelodysplasia by the presence

of > 30% blasts in bone marrow cells or circulating white blood cells; experts have revised this to > 20% blasts.

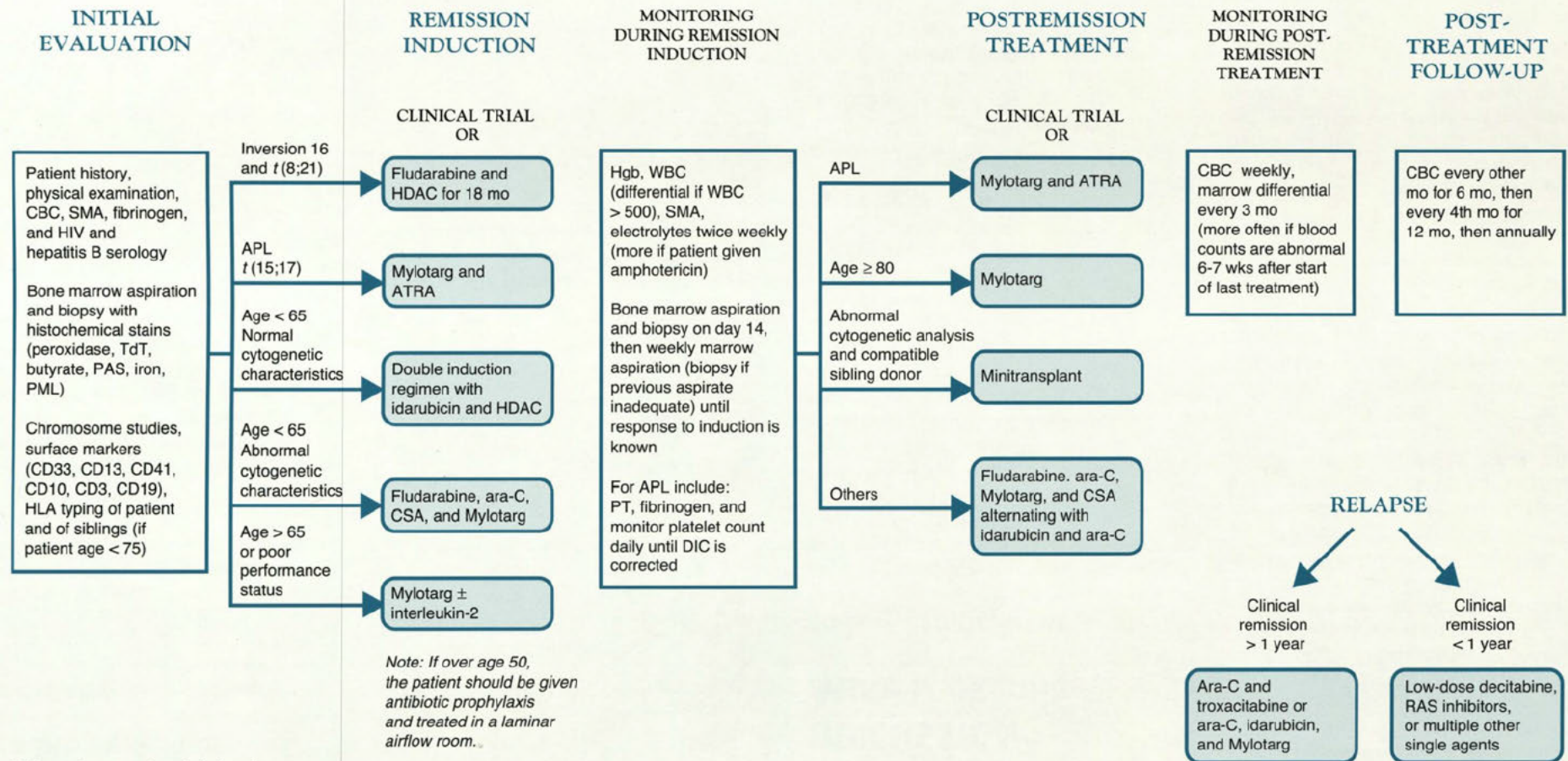
Patients with marrow dysfunction and dysplasia are said to have MDS. Those whose blast counts are 6%-19% are said to have "refractory anemia with excess blasts" (RAEB), a form of MDS. MDS has also been called "preleukemia" because patients are considered to be at high risk for the development of AML within 12 to 24 months. However, says Dr. Estey, this term is very misleading, as it implies that MDS is only risky because it may lead to AML when, in fact, MDS is a potentially fatal condition itself. Patients with RAEB tend to be very ill. Without treatment, half of them will die within a year, and it is rare for these patients to live as long as two years.

The karyotype of the leukemic cell is an extremely important determinant of both prognosis and treatment. Three subsets of AML are well known and important to identify. They are the cytogenetic abnormalities "Inversion 16" and *t*(8;21) and APL, which is defined by the *t*(15;17) abnormality. These subgroups have more favorable prognoses than subgroups with other abnormal karyotypes. Patients with normal cytogenetic characteristics

(Continued on next page)

Adult AML and High-Risk MDS (RAEB-t, RAEB)

 Treatment



- AML Acute myelocytic leukemia
- APL Acute promyelocytic leukemia
- ATRA All-trans-retinoic acid
- CSA Cyclosporin A
- DIC Disseminated intravascular coagulation
- HDAC High-dose ara-C
- MDS Myelodysplastic syndrome
- RAEB Refractory anemia with excess blasts
- RAEB-t RAEB in transformation

For available programs and treatment priorities and to view the newsletter *Leukemia Insights*, visit the Department of Leukemia Web site at: <http://www.mdanderson.org/~leukemia>.

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generally have more favorable prognoses than those with abnormalities other than APL, *t* (8;21), or Inversion 16.

Other important prognostic factors guiding treatment include age and overall health, which affect the patient's ability to tolerate intensive systemic therapies.

Initial Evaluation

AML is most often discovered upon clinical evaluation of patients presenting with symptoms related to bone marrow infiltration (e.g., anemia, persistent infection, fatigue, and pallor), coagulopathies (such as disseminated intravascular coagulation [DIC], caused by the release of procoagulants), or organ involvement (e.g., infiltrative gastrointestinal or mesenteric lesions or obstructive hepatobiliary or genitourinary lesions) caused by the accumulation of blasts (leukostasis).

Abnormal CBC findings (occasionally, marked elevation in WBC but more often pancytopenia) may cause one to suspect leukemia, but a definitive diagnosis is made by pathologic evaluation of bone marrow. This evaluation should include morphology, histochemical staining, cytochemistry, immunophenotyping by fluorescence-activated cell sorting using monoclonal antibodies specific for leukemia antigens (which analyzes cell surfaces for cluster-designation markers specific to monoclonal antibodies), and cytogenetic analysis. Other tests may be indicated to evaluate metabolic abnormalities, organ involvement, or coagulopathies.

Human leukocyte antigen (HLA) typing of patients and their siblings should be included for patients who may be candidates for allogeneic bone marrow transplantation. The decision to perform a transplant must

be considered in the context of patient and donor age and general health, as well as patient preferences and attitudes and whether the procedure is feasible for them.

According to all of our experts, it is extremely important to correctly identify specific karyotypes in AML, because these define subsets of patients with specific prognoses and, in some cases, treatments.

Initial Induction

The goal of initial therapy for all patients with AML is to bring about a remission of disease, which is defined as a normal blood count with $\leq 5\%$ blasts.

Approximately 5%-10% of patients with AML have the Inversion 16 cytogenetic abnormality. Initial treatment for this group of patients is fludarabine plus high-dose cytarabine (ara-C) for 18 months. "We see a complete remission rate of about 90% and a cure rate of greater than 50% with this regimen for this group," says Dr. Kantarjian.

Patients with the *t* (8;21) cytogenetic abnormality are also treated with fludarabine and high-dose ara-C for 18 months.

Another 5%-10% of patients with AML will present with the APL subtype. This abnormality is characterized by the *t* (15;17) translocation, which disrupts fusion of the retinoic acid receptor (RAR) on chromosome 17 with the promyelocytic leukemia (PML) gene on chromosome 15. The clonogenic cell in APL is derived from the CD33 compartment, whereas in other subtypes of AML, stem cells originate from a subcompartment of CD34. DIC develops in a high percentage of patients with APL because of the release of procoagulation factors by abnormal cells. Prior to the discovery of specific cytogenetics and targeted agents, DIC was responsible for most of the deaths in this category

of leukemia, and many patients died of the disorder within weeks. Treatment agents for patients with APL include all-*trans*-retinoic acid (ATRA), which corrects the clotting deficiency, and Mylotarg, a monoclonal antibody specific for the CD33 subcompartment and one of the first of a new class of anticancer agents. Today, experts cite a $> 90\%$ clinical remission rate with this treatment. Dr. Andreeff believes that these new anticancer agents represent "one of the great breakthroughs in medicine."

For all other patients with AML, treatment decisions are directed by factors such as age and overall health, which may affect the patient's ability to tolerate certain therapies.

Patients younger than 65 years of age with no cytogenetic abnormalities are treated with idarubicin and high-dose ara-C (HDAC) given in a "double induction" regimen. This regimen consists of two time-sequenced cycles; the second cycle targets previously quiescent leukemic stem cells as they become active and thus susceptible to chemotherapy.

Patients younger than 65 years whose cytogenetic study results are abnormal are given induction therapy consisting of Mylotarg plus chemotherapy using fludarabine, ara-C, and cyclosporin A (CSA).

For patients older than 65 years and those who have a poor performance status or comorbid medical conditions, Mylotarg plus interleukin-2 is being investigated as an alternative to more intensive chemotherapy regimens, which are associated with high mortality rates in these patients.

For all patients older than 50 years of age, a protected environment (laminar airflow room) and a prophylactic triple antibiotic regimen are recommended as well, as these have been shown to reduce morbidity and mortality rates by 50% in this age group.

Close surveillance is appropriate during induction therapy and should include blood laboratory studies as shown in the guideline, bone marrow aspiration and biopsy on day 14 of treatment, and weekly aspiration thereafter until the response to induction therapy is known. The biopsy should be repeated if the aspirate is inadequate.

Postremission Treatment

After remission has been achieved, our experts recommend consolidation therapy to maintain remission response, except in patients with Inversion 16 or *t* (8;21) abnormalities, who receive fludarabine and ara-C for 18 months.

Postremission treatment for patients more than 80 years old consists of single-agent Mylotarg for six months. Patients with APL receive additional courses of therapy with Mylotarg and ATRA for nine months.

Patients who have other cytogenetic abnormalities represent a higher-risk group, and for those who have an HLA-compatible sibling donor, allogeneic bone marrow transplantation has traditionally been a consideration. However, the "mini-transplant" currently in use at M. D. Anderson is a less intensive intervention in which stem cells from blood rather than marrow are transplanted, accompanied by non-myeloablative immunosuppressive chemotherapy consisting of fludarabine, ara-C, and mitoxantrone (FLAM). It was previously thought that chemotherapy had to be myeloablative to be effective, but according to Dr. Andreeff, the immunosuppression achieved by fludarabine is sufficient to allow for engraftment and exertion of a graft-versus-leukemia effect. Dr. Estey emphasizes, "The real benefit is that we can now offer this treatment to patients who would not be able to

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tolerate the more intensive approach." Minitransplants have been successful in patients up to 75 years old who would not have been candidates for a traditional bone marrow transplant.

Postremission or consolidation therapy for all other patients consists of combination chemotherapy such as fludarabine, ara-C, Mylotarg, and CSA alternating with idarubicin and ara-C for one year.

Surveillance during postremission treatment consists of weekly CBCs and marrow differential tests every three months. These should be done more frequently if blood counts become abnormal within six to seven weeks after starting this treatment.

Posttreatment Follow-up

When treatment is complete, surveillance should include CBCs at least every other month for six months, then every fourth month for a year if findings are normal. Thereafter, if findings remain normal, the patient should be monitored annually.

Relapse

Relapse after treatment for AML is a challenging clinical problem. In most cases, the length of clinical remission is the most influential factor guiding treatment decisions for patients whose disease reappears. In patients whose clinical remission lasted more than a year, response to the initially used agents is more likely; for those whose remission was shorter, their disease might be considered resistant to the initial agents, and different agents are sought.

Authors' Perspectives

Leukemia is a disease in which treatment advances are made at the molecular level. Several advances in the treatment of leukemia are considered "medical breakthroughs."

Researchers have identified defects in the clotting cascade and have learned how to correct them with specific agents. They have found the stem cell subcompartments where malignant cells arise and have devised a way to send a cytotoxic agent directly there—"Trojan-horse style"—in a monoclonal antibody carrier specific to that subcompartment. And they have discovered a method of transplanting stem cells that older people can tolerate. Despite these stunning advances in the treatment of leukemia, however, the word "cure" is seldom used in this circle of physicians, even though more patients are cured of leukemia than of any other cancer. Instead, they are looking ahead to new advances that will help to explain why certain therapies work and others do not and that will result in gentler courses of treatment. All of our experts agree that clinical trials are currently the best options for the treatment of patients with all categories of AML. In spite of the major advances in the treatment of this disease, there are still many unknowns. According to Dr. Estey, a certain proportion of patients will have recurrent disease despite any given therapy, so it is important to provide several treatment options and to know more about how and why they work. And, in view of the older age group affected by this disease, the search must continue for agents that are less toxic.

Current research is aimed at delineating novel stem cell phenotypes for AML and further exploiting the molecular abnormalities found in leukemic cells to develop more molecular-based therapies. One such line of investigation centers on apoptosis of leukemic cells, where the problem is not proliferation of cells but rather that the cells do not die, or undergo apoptosis, in a normal way. Novel approaches are under development: one is aimed at overcoming roadblocks to chemotherapy-induced apoptosis; another aims to restore normal differentiation pathways in leukemic cells that would result in the maturation and eventual death of AML cells.

Find more information about clinical trials and current protocols available at M. D. Anderson at <http://www.mdanderson.org/research/>.

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