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REPORT TO PHYSICIANS

JULY/AUGUST 2006 Vol. 51, No. 7-8

OncoLog

Gaining Momentum in *MDS*

In two short years, major advances have changed the clinical treatment of myelodysplastic syndrome, and more advances may be close behind.

by **Dianne C. Witter**

Elihu Estey, M.D., gestures to the survival curve on his computer screen as he talks; it's a cautionary graphic to temper our discussion of the unprecedented recent advances in the treatment of myelodysplastic syndrome (MDS), a rare—and often fatal—disease of the bone marrow.

Over the years, the steep downward slope of the curve hasn't improved much. But recent advances in scientific knowledge about the biology of the disease, which led to important treatment advances, have given even a self-avowed skeptic like Dr. Estey renewed expectations.

A professor and section chief for MDS and acute leukemias in the Department of Leukemia at The University of Texas M. D. Anderson Cancer Center, Dr. Estey said, "Historically, MDS has been resistant to treatment, and the prognosis for most patients has been poor. Other than bone marrow transplants or acute myeloid leukemia-type chemotherapy for the small minority of patients who qualified, supportive care or clinical trials were the only treatment options."



What a difference two years can make. Today, there are three new, FDA-approved drugs that are putting many more patients into remission. More very promising drugs—and combinations of drugs—are in clinical trials now. M. D. Anderson has played a key role in these advances, thanks in part to one of the largest MDS patient bases in the world.
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MDS is one of the most common—if lesser known—subtypes of leukemia, and the incidence continues to rise, said Dr. Elihu Estey.

THE UNIVERSITY OF TEXAS
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Gaining Momentum in **MDS**

(Continued from page 1)

Here, we give a brief overview of the current state of MDS research and treatment.

A new class of drugs

An improved understanding of the molecular biology of the disease was key to the development of the first non-intensive therapy to have a significant impact on the course of MDS. A new class of drugs, DNA methyltransferase inhibitors, restores normal function to silenced genes that ordinarily suppress the development of MDS. Azacitidine (Vidaza) was the first such drug to receive approval for use in MDS, in May 2004, ushering in a new wave of scientific interest and generating optimism about a disease that, previously, was known only for its poor outcomes.

M. D. Anderson investigators were already conducting studies of decitabine (Dacogen), a similar but more potent drug. Laboratory investigators led by Jean-Pierre Issa, M.D., a professor in the Department of Leukemia, championed the idea that this drug's mechanism of action might make it more effective when administered at very low doses for a longer period of time. Studies proved the hunch to be correct. "This was a remarkable phenomenon that would have been missed if we had simply focused on identifying the maximum tolerated dose," said Dr. Issa.

Hagop Kantarjian, M.D., a professor and the chair of the Department of Leukemia, agrees. "Decitabine was effective in MDS at a fraction of the chemotherapy dose, and without the hematological toxicity," he said. The multi-institution studies led by Dr. Kantarjian and his colleagues demonstrated a complete response rate of almost 40% and an objective response in as many as 70% of participants.

Decitabine received fast-track approval from the FDA in May, but studies of

different dosing schedules continue in an effort to further improve outcomes. "I don't think the best dosing schedule for either decitabine or azacitidine has been identified yet," Dr. Kantarjian said. "If we can perfect that, we might see a substantial impact on prognosis."

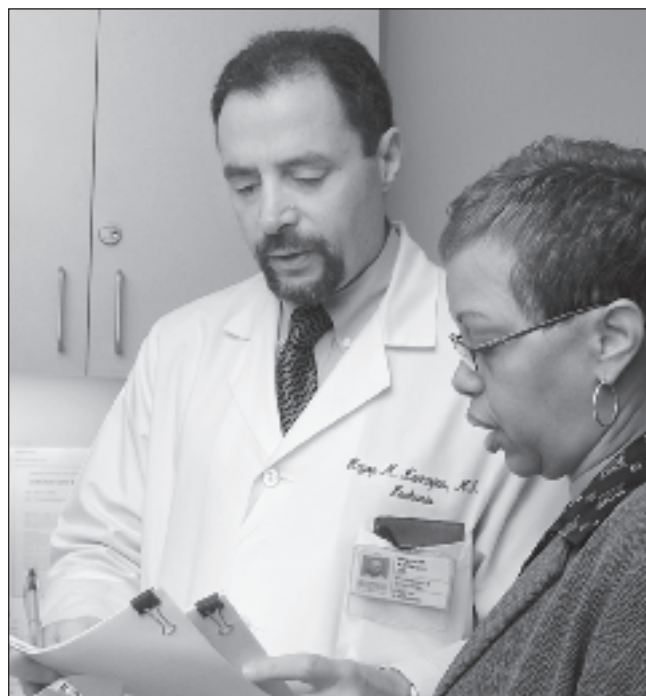
Another drug recently approved for use in a subtype of MDS is lenalidomide (Revlimid), a thalidomide analogue with fewer side effects. In patients whose bone marrow has the 5q- cytogenetic characteristic, historically one of the subgroups with the poorest prognosis, lenalidomide brought about major hematologic responses in a majority of patients.

Currently, the only curative treatment for MDS remains a bone marrow transplant or chemotherapy similar to that typically given to patients with acute myeloid leukemia, but in both cases the risks outweigh the possible benefits for many older patients. The

advent of the "mini-transplant," a non-myeloablative procedure, has made stem cell transplants viable for more patients, including those over 60 years old.

The recent approval of a once-daily oral iron-chelating agent, desferasirox (Exjade), is a welcome quality of life advance

for people with iron overload due to repeated blood transfusions. Previously, daily iron chelation was usually self-administered by patients subcutaneously via an external pump worn for 8 to 12 hours—inconvenient and therefore an



Dr. Hagop Kantarjian and colleagues championed the use of low-dose decitabine in MDS and were integral in its approval last May. Here, Dr. Kantarjian and **Lajuanda Williams, R.N.**, confer during clinic.

impediment to compliance over weeks or months of therapy.

Continuing the momentum

The recent metamorphosis in the treatment of MDS may be just a preview of things to come. With research funding for the disease at an all-time high (although still low compared with other diseases), the pace in this field has quickened considerably.

Last year, M. D. Anderson was awarded the largest-ever federal grant specifically for MDS research, a \$10 million commitment that funds an expansive research program and brings together top scientists from a number of institutions in studies ranging from the laboratory to the clinic.

"One of our key objectives is to look at what abnormalities come together to develop MDS," explained Dr. Estey, who is principal investigator for the grant. "One way we're doing that is by establishing a multi-institution tissue bank that we'll sample serially over time to look at epigenetic changes and other characteristics." He noted that the issue of methylation is key in laboratory research on MDS.

Also key in laboratory research is a mouse model of the disease—which

“It’s a disease of the bone marrow stem cells in which chromosome abnormalities compromise the ability of stem cells to mature into healthy, functional blood cells.”

– Dr. Elihu Estey

doesn't exist yet for MDS. "Once we have more information about the make-up of MDS, another focus will be to develop an accurate mouse model," Dr. Estey said.

Another emphasis of the grant is clinical discovery and testing of new drugs for MDS. For instance, investigators testing a promising vaccine developed at M. D. Anderson will begin enrolling low-risk MDS patients in a phase II study this fall. This proteinase 3 PR1 peptide vaccine initially showed surprising success in patients with refractory acute myeloid leukemia, and it has shown promise for MDS as well.

Following up on the success of the hypomethylating agents decitabine and azacitadine, investigators are now looking at other drugs that may work synergistically with these drugs. "MDS is an exciting disease to study right now," said Dr. Kantarjian. "With our improved understanding of the biology of MDS, we're looking at using older drugs in a new, more effective way. For instance, the histone deacetylase inhibitor valproic acid is being studied in combination with decitabine, as are suberoylanilide hydroxamic acid and others." There are a number of new agents under study as well, including the antineoplastic agent clofarabine and AMG531, a platelet stimulator.

The field of MDS has undergone unprecedented transformation in recent years. In the lab, scientists are developing a better understanding of how we might alter the genetic underpinnings of the disease. In the clinic, new medications developed as a result of this knowledge are offering patients greater chance of remission, improved quality of life, and freedom from blood transfusions.

The stark statistics of MDS are still daunting, and the survival curve is just as steep. But real ground has been gained, and patients now have a fighting chance. The prognostic outlook, as Dr. Estey might say, is 'cautiously optimistic.' ●

FOR MORE INFORMATION, contact Dr. Estey at (713) 792-7544, Dr. Issa at (713) 745-2260, or Dr. Kantarjian at (713) 792-7026, or visit www.mdanderson.org/departments/leukemia.

When Bone Marrow Goes Awry

Blood cell production can be hampered by any number of causes, many of them minor and easily remedied. In myelodysplastic syndrome (MDS), however, the situation is much more complicated and difficult to treat. "It's a disease of the bone marrow stem cells in which chromosome abnormalities compromise the ability of stem cells to mature into functional blood cells," explained Dr. Elihu Estey. "In MDS, the marrow becomes populated by immature cells, or blasts, and cytopenias develop."

As a result, regular blood transfusions are often a necessity. Low platelet counts put patients at risk for life-threatening hemorrhage. Low white blood cell counts, particularly neutrophils, set patients up for opportunistic infections that may be resistant to treatment.

The course of MDS is variable, but it is progressive. Without treatment that delays progression, about three-fourths of MDS patients die within two to three years of diagnosis; in the high-risk category, the prognosis is more like six to 12 months. But current treatments for MDS are significantly better than supportive care—the previous standard treatment—and survival curves may soon reflect that.

In about 30% of patients, MDS transforms into acute myeloid leukemia (AML), said Dr. Estey, which is why it has often been referred to as "pre-leukemia." "That's a misnomer, though," he said. "MDS can be, and often is, fatal before AML ever develops, and AML doesn't develop in everyone with MDS."

Subtle signs

The first clinical signs of MDS are unremarkable and thus easily missed. Pallor and excessive fatigue are the most common, sometimes accompanied by bruising, petechiae, or increased infections. Anemia is often the most salient initial finding, which scarcely narrows the diagnosis.

As a result, MDS is often misdiagnosed or not diagnosed at all. It doesn't help that MDS is largely a disease of people over 60 years old. "Many doctors feel anemia is a normal

part of aging," said Dr. Estey. He feels this belief leaves many people undiagnosed and untreated until their disease progresses.

Dr. Estey suggests that the cause of a low hemoglobin level is always worth investigating. "Someone could have a very significant illness with a hemoglobin that's just a little low," he said.

Given the complexity of MDS and the relative rarity of the disease, a definitive diagnosis usually requires referral to a cancer center or to a specialist in hematology or oncology. When a physician has determined that a patient's anemia is not due to simpler explanations—such as iron or B12 deficiency—other findings may suggest MDS. For instance, suppression of white blood cells and/or platelets in addition to red blood cells could indicate MDS, as could abnormalities in the shape and size of the red blood cells. Ultimately, diagnosis of MDS requires a bone marrow biopsy, with cytogenetic analysis of the tissue.

"As the population ages, community physicians can expect to see more patients with MDS," said Dr. Estey. "It's considered a rare disease, but it's probably the most common subtype of leukemia, with about 13,000 cases diagnosed per year."

Ironically, the fact that more people are surviving cancer today than ever before has also contributed to the rising incidence of MDS—chemotherapy and radiation can damage the bone marrow and lead to therapy-related MDS in some patients. ●



Dr. Estey (r) and Dr. Jean-Pierre Issa discuss DNA methylation studies in Dr. Issa's laboratory.

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MDS PROTOCOLS

High-risk MDS

- Phase II study of decitabine administered daily for 5 days every 4 weeks to adults with advanced-stage MDS (2005-0941). Physician: Hagop Kantarjian, M.D.
- Phase II randomized study of three different schedules of low-dose decitabine in MDS (ID03-0180). Physician: Hagop Kantarjian, M.D.
- Phase I/II study of the combination of 5-azacytidine with valproic acid and all-trans retinoic acid in patients with high-risk MDS and AML (2004-0799). Physician: Guillermo Garcia-Manero, M.D.
- Phase II randomized study of two different schedules of intravenous clofarabine in MDS (2005-0535). Physician: Hagop Kantarjian, M.D.

Low-risk MDS

- A multi-center, open-label study of the efficacy and safety of FG-2216 in lower-risk MDS (2005-0721). Physician: Hagop Kantarjian, M.D.
- An open-label, sequential cohort, dose escalation study to evaluate the safety and efficacy of AMG 531 in subjects with thrombocytopenia and low- or intermediate-1-risk MDS (2005-0577). Physician: Hagop Kantarjian, M.D.
- A multi-center, open-label, phase I study of GX15-070MS administered weekly to patients with AML, MDS, chronic myeloid leukemia in myeloid blast phase, myelofibrosis, or previously-treated chronic lymphocytic leukemia (2005-0584). Physician: Hagop Kantarjian, M.D.

Additional studies

- Phase II study of low-dose decitabine in MDS post-azacitidine failure (2004-0468). Physician: Hagop Kantarjian, M.D.
- Randomized phase II study of clofarabine alone vs. clofarabine in combination with low-dose cytarabine (ara-C) in previously untreated patients \geq 60 years with AML and higher-risk MDS (2004-0183). Physician: Stefan Faderl, M.D. ●

FOR MORE INFORMATION, visit www.clinicaltrials.org, or call (800) 392-1611 or (713) 792-3245.

Pancreatic Cancer: It Takes a Village

by Sunni Hosemann

Pancreatic cancer is known to be an intractable and aggressive cancer, and its reputation is well-deserved. Although there are several types (and some exotic subtypes), the most typical—95%—are exocrine adenocarcinomas. They are especially difficult cancers to diagnose and treat because they usually give no early signal to herald their presence, no definitive symptom to alert patient or physician that something is very wrong. Anatomy doesn't help the situation: the pancreas lies deep within the body, making imaging difficult, and it is an organ rife with vital vessels and ducts that make tumor excision tricky. Thus, most pancreatic cancers are quite advanced by the time they are discovered and are difficult to treat.

"Survival rates for this cancer are low and haven't changed dramatically in the past decade, except for patients who have surgery," said James Abbruzzese, M.D., a professor and chair of M. D. Anderson's Department of Gastrointestinal Medical Oncology. "We haven't seen the major shift we'd like to see." But, he notes, bringing about that shift is the passion of many scientists and physicians at M. D. Anderson who are collaborators in the Pancreatic Cancer Study Group, a program remarkable for the number of people involved and the diversity of disciplines represented—laboratory scientists, epidemiologists, imaging specialists, medical oncologists, and more. This group has a clinical and research agenda that is at the same time broad and focused: no gene or cell signal



A strong team focus is key to the Pancreatic Cancer Study Group's success, according to **Dr. James Abbruzzese** (page 5, left). Shown here are two of the many collaborators on the team: **Dr. Jeffrey H. Lee** (page 5, right), and **Dr. Jeffrey E. Lee** (above).

is unexamined, no minor tweak too unimportant, but all are focused on the larger goal as well. It is a team with a true translational research mindset, in which each contribution is interdependent on others and all members place a high value on collaboration.

The best tools today

Surgery—pancreaticoduodenectomy—is still the only measure for pancreatic cancer that can be curative. Patients

Tackling one of the toughest kinds of cancer takes a team of diverse specialists working from every angle. Enter the Pancreatic Cancer Study Group at M. D. Anderson Cancer Center.



who are candidates for the surgery are the ones more likely to survive. This operation—also known as a Whipple procedure—is a very serious and lengthy surgery, taking anywhere from 5 to 10 hours. A decade ago, the mortality rate for the operation alone was about 25%, but that has totally changed. “Now, it is uncommon for a patient to die following this surgery at a major center,” said Jeffrey E. Lee, M.D., a professor in the Department of Surgical Oncology.

But surgical advances, said Dr. Lee, are by no means the only significant factors. Better perioperative care—including preoperative medical assessment and anesthesia and support from specialties such as endocrinology, nursing, and nutrition service—help account for the significant reductions in both morbidity and mortality. In Dr. Lee’s view, advances in the preoperative workup—leading to better identification of patients who can successfully undergo such a major operation and are most likely to benefit from surgery—have been critically important. “We want to be as certain as possible that patients selected for this

surgery do not have evidence of metastasis and that we can completely remove the tumor,” said Dr. Lee. “Our ability to do that is largely due to an improvement in the quality of preoperative imaging studies,” he said.

Eric Tamm, M.D., an associate professor in the Department of Diagnostic Radiology, describes new imaging technologies developed at M. D. Anderson that yield rapid scans, thinner slices, and smooth, “exquisite” images. “It’s like the difference between a light bulb and a searchlight,” he said. In addition to state-of-the-art equipment, he cites a new 64 detector-row helical computed tomography (CT) scanner as an example. He and his colleagues are testing software that allows the images to be viewed in planes different from those in which they were scanned. This is particularly useful in pancreatic cancers because it allows for a thorough search for tumor-caused distortions in critical veins and arteries that may not otherwise be visible. The extent and location of vessel involvement are critical determinants of operability.

A preoperative roadmap

At M. D. Anderson, the helical CT scan is the initial staging procedure for a patient with suspected pancreatic cancer. “We try to do it first, to have a baseline image before any manipulation that could cause inflammation in the organ,” said Dr. Tamm. The next common step in the workup is endoscopic ultrasound (EUS). A skilled endoscopist can precisely document the pancreatic lesion, search for smaller tumors that may have evaded CT detection, examine nearby vessels and lymph nodes, and look for evidence of local and metastatic disease spread.

Jeffrey H. Lee, M.D., an interventional endoscopist, who is an associate professor in the Department of Gastrointestinal Medicine and Nutrition, says that the combination of CT and EUS is “synergistic”—that together, they provide a thorough preoperative overview. At M. D. Anderson, an EUS is performed simultaneously with an endoscopic retrograde cholangiopancreatography. Here, the endoscopist can obtain a tissue sample by fine-needle aspiration and can also place stents in tumor-occluded bile ducts to relieve the obstructive jaundice that is usually present.

According to Dr. Jeffrey H. Lee, the combined power of these imaging tools helps the treatment team make decisions about surgery for a given patient. “For patients who will have surgery, it helps determine whether neoadjuvant therapy (usually chemoradiation) could

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“Pancreatic cancer is one of the toughest problems in solid tumor oncology.”

– Dr. Jeffrey E. Lee

Pancreatic Cancer

(Continued from page 5)

be helpful and becomes a roadmap for the surgeon,” he said. For all patients, it provides staging that once had to be done surgically and more accurately pinpoints who is most likely to benefit from surgery. As the techniques become more advanced, the stage of disease can be more precisely defined and treatment tailored to the extent of the cancer in a specific patient.

One surgical advance popularized by M. D. Anderson involves the removal and replacement of blood vessels close to the pancreas that can prevent complete tumor removal. Patients whose tumors do not involve major arteries but do involve the superior mesenteric or portal vein may have the tumor removed and the veins reconstructed. “Our group helped develop criteria to select patients for this technique and refined the surgical procedures to allow successful tumor removal under these circumstances,” noted Dr. Jeffrey E. Lee. “We have found that these patients can do as well as those who did not require the resection.”

More questions than answers

“Still,” said Dr. Jeffrey E. Lee, “pancreatic cancer is one of the toughest problems in solid tumor oncology, and even patients who are candidates for surgery remain at high risk for recurrence.” Because of that, clinical work is ongoing to try to determine the best combination of treatments to use either in conjunction with surgery, when possible, or instead of surgery.

Today, the enrollment of patients with pancreatic cancer into clinical trials has dramatically increased. Currently at M. D. Anderson, there are clinical trial options for patients with every stage of disease. In addition, novel systemic therapies are being studied as more is learned about the mechanisms of the disease; examples include tyrosine kinase inhibitors, antiangiogenic agents, and vaccines. One interesting example of a novel agent is curcumin, which is currently being evaluated in a phase I

trial. This compound, found in the spice turmeric, acts to suppress the transcription factor NF-kappa B, which is constitutively activated in pancreatic cancer. Studies are also under way of other agents that target NF-kappa B, as well as agents that target other transcription factors. For example, a clinical trial will soon open involving dasatinib, an inhibitor of the protein

The pancreas is an organ rife with vital vessels and ducts that make tumor excision tricky. One surgical advance involves the removal and replacement of certain blood vessels close to the pancreas to allow for complete tumor removal.

tyrosine kinase Src, which is aberrantly activated in 70% of pancreatic cancers.

There are other promising therapies in the pipeline, and discoveries are moving quickly from the laboratory into the clinic, as evidenced by the efforts of the Pancreatic Cancer Study Group at M. D. Anderson. However, at present, treatment must be highly individualized. For this reason, many physicians agree that patients with pancreatic cancer are best served by treatment in a major cancer center and, when possible, as part of a clinical trial.

Eye on the future

The research agenda in pancreatic cancer is broad. It is looking for better treatments and a better understanding of who gets this disease and why and how it might be found earlier. M. D. Anderson’s receipt of the National Cancer Institute Specialized Programs of Research Excellence (SPORE) grant for pancreatic cancer brings together a diverse team of scientists to study the equally diverse aspects of this disease, from laboratory research to clinical trials. Thus, one of the focal points of the pancreatic cancer grant is the Tumor Bank and Database. Tissue and fluid samples from every possible procedure—surgery, biopsies, endoscopy—are saved and logged, along with correlating

clinical information. The result is a growing compendium of vital information that can be accessed by scientists studying pancreatic cancer. Another important data collection effort is gathering epidemiologic information aimed at answering the question, Who is at risk for this disease?

The most consistently identified epidemiological risk factor for pancreatic cancer is cigarette smoking; fully one-third of pancreatic cancers occur in smokers. There also seem to be potential relationships between the development of pancreatic cancer and other environmental carcinogens—radiation and hydrocarbon solvents, for example. These kinds of data will add a critical dimension to the laboratory and clinical studies that look into the questions of how carcinogens are metabolized—something that may differ among individuals. Epidemiological studies will also shed light on the importance of family history and heredity, because certain hereditary conditions have known associations with pancreatic cancer, as do genetic point mutations or amplifications, overexpression of oncogenes, and alterations of tumor suppressor genes. Thus, harvesting and organizing family and health history information are important.

The Pancreatic Cancer Study Group epitomizes what it means to do translational research. For now, and for the future, they are staying focused on the smallest details of their work, but they are also mindful of how their findings might bolster the work of colleagues in another discipline—and all with an eye on the broader goal of ultimately conquering pancreatic cancer. ●

FOR MORE INFORMATION about the Pancreatic Cancer Study Group and clinical trials for pancreatic cancer, go to www.mdanderson.org/diseases/pancreas
Other good resources:
www.pancreatica.org
www.cancer.gov/cancerinfo/types/pancreatic



Tired of Being Tired

Communicating with your doctor about fatigue is an important first step in managing it.

What's the most common and distressing symptom cancer patients face? Pain? Nausea? No, it's fatigue.

"I always emphasize this fact to patients," said Ellen Manzullo, M.D., a professor in the Departments of General Internal Medicine, Ambulatory Treatment, and Emergency Care as well as co-director of M. D. Anderson's Fatigue Clinic. "People are usually relieved when I say it because they feel like their symptom has been validated. I think they get some comfort in knowing that they are not alone."

"At M. D. Anderson, about 50% of patients with blood-related cancers have severe levels of fatigue, as do about one-third of those with solid tumors," said Shelley Wang, M.D., an assistant professor in the Department of Symptom Research. In some cases, fatigue can be a presenting symptom; in other cases, however, it is not.

Another point worth emphasizing, said Dr. Manzullo, is that not all fatigue is physical—mental fatigue can be part of the whole complex as well. Unrecognized, fatigue can become much more than an annoyance; it can actually impair the person's daily life and may even have an impact on treatment success. Still, it is one of the least-discussed aspects of cancer. Why?

Communicating is key

"When we talked to patients," said Charles Cleeland, Ph.D., head of Symptom Research at M. D. Anderson, "they said they don't tell their doctors about their fatigue because nothing can be done about it."

In the meantime, not recognizing and managing fatigue early can have serious consequences. "Not identifying it leads to physical deconditioning, isolating oneself from family and friends, and other factors that contribute to poor outcome. If cancer treatment is causing the fatigue, the problem may become so unmanageable that the patient stops



TIPS

for coping with fatigue

- Drink plenty of liquids, especially water and fluid replacement drinks with electrolytes.
- Eat frequent small meals.
- Snack on foods high in protein.
- Consider liquid meal replacements such as Boost and Ensure when you don't have the energy to prepare something.
- Take short, frequent rests (no more than 30 minutes) throughout the day, rather than one long nap.
- Follow a nap with an activity or quick exercise, like a short walk.
- Take part in activities/hobbies that are not strenuous.
- Schedule priority activities during peak energy times, and scale back on other commitments.
- Learn to say "no."

treatment for awhile, which could impact survival," Dr. Cleeland added.

It's important to talk to your doctor if you are feeling fatigued. "There have been some studies that suggest that if physicians have information about a symptom available at the time of the consult, then they are more likely to do something about it," said Dr. Cleeland. "If patients don't report symptoms, then

the physician will never know to treat them. There are things that can be done, but nothing is going to be done if you don't tell someone."

An objective measure

To help simplify and encourage communication about symptoms, physicians at M. D. Anderson have developed the Brief Fatigue Inventory (BFI), which allows patients to rate the severity of several fatigue-related symptoms on a 0-10 scale. Because the BFI uses numeric ratings, it provides a simple, non-language-based way to indicate the patient's level of fatigue.

"Many dimensions of fatigue can be measured," noted Dr. Cleeland. "The most important ones that we have incorporated in the BFI are how much fatigue a patient is feeling and how much of an effect it has on daily life. The BFI is an attempt to help patients think of these symptoms as measurable, as much as blood pressure and other clinical factors." This gives patients and their doctors a more objective way to talk about the problem and see changes over time.

A sample of BFI can be found at www.mdanderson.org/topics/fatigue, or you can informally rate your fatigue on a scale of 0-10. The information can serve as a means of initiating conversations about fatigue between patients and their family members or doctors—communication that is the first, crucial step in dealing with fatigue. ●

For more information, talk to your physician, or:

- call the M. D. Anderson Cancer Center Information Line at (800) 392-1611 (Option 3) within the United States.
- visit www.mdanderson.org.

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K. Carnes

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DiaLog

Anemia in the Elderly

Elihu Estey, M.D.
Professor, Department of Leukemia



A study in the April 2006 issue of the *American Journal of Medicine* (AJM) found that 24% of people over 65 years old were anemic, but it discouraged the practice of ascribing the cause of anemia simply to older age. (Anemia was defined as a hemoglobin level below 12 g/dl in women and 13 g/dl in men.) As a physician with an interest in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), I'm probably oversensitized to the possibility of these serious diagnoses in older patients with anemia, but the incidence of AML and MDS does rise significantly with age, and all physicians should be aware of this.

The AJM study showed that anemia increased the risk of death by 40%, after accounting for age, body mass index, kidney function, and other indicators of general health. Furthermore, deficits in cognition were much more frequent in people with anemia.

The AJM paper confirms the importance of diagnosing and managing anemia and points out that, although common, anemia is not normal in the elderly, i.e., most of the elderly are not anemic. Many conditions can cause anemia; these conditions run from the mundane (dietary folic acid deficiency) to the life-threatening (MDS and AML). Thus, the cause of anemia has a strong influence on mortality and should be routinely investigated, even in very old patients.

The starting point for diagnostic evaluation of anemia in the elderly is the patient history. This, for example, might indicate that the patient is taking a medicine that can cause anemia. Even non-prescription drugs such as ibuprofen can be responsible by causing blood loss from the gastrointestinal tract. The most important laboratory test is the reticulocyte count. A high count suggests that the cause of anemia is excessive destruction of red blood cells and that the bone marrow is responding appropriately to the anemia. Conversely, a low reticulocyte count suggests that marrow failure underlies the anemia. If a search for iron, B12, folic acid, or erythropoietin deficiency is unrevealing, examination of the bone marrow is in order.

MDS can be diagnosed when more than 5% of the cells are immature cells (blasts) or when there is a cytogenetic abnormality. When the blast count is from 10% to 20%, the distinction between MDS and AML is quite blurred; when it exceeds 20%, the diagnosis is AML. Because hematopathologists often differ in their identification of mild-to-moderate dysplasia, caution should be exercised in diagnosing MDS when the blast count is below 5%, when cytogenetic abnormalities are absent, and when only mild-to-moderate dysplasia is present. More sensitive and specific tests to diagnose MDS will almost certainly be based on the identification of genetic abnormalities.

Because of the availability of new treatments that can reduce the need for transfusions, identifying and treating MDS is more important now than ever before. ●

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