

## FEATURE STORY

# Treatment Boost for MDS

BY ALICE MCCARTHY

*Deep in the bone marrow lies the reason for blood disorders classified as myelodysplastic syndromes—stem cells gone awry.*

In the mid-1970s, a group of pathologists and clinicians from around the world gathered several times to discuss a set of blood disorders with a strong resemblance to leukemia but with notable differences. Known as the French-American-British (FAB) Cooperative Group, this assembly created a classification in 1976, which it refined and expanded in 1982, that defined myelodysplastic syndromes (MDS).

The designations gave doctors the ability to better diagnose and treat MDS patients. But even as doctors were able to better classify MDS, patients were still without effective treatments. That's not quite true anymore. In the past two years, the Food and Drug Administration approved several therapies, and others are undergoing testing, offering some patients the prospect of a better quality of life, and possibly changing the natural course of the disease.

Chet Hodge, a 71-year-old aerospace engineer from Mesa, Arizona, was diagnosed five years ago with a mild form of MDS and felt wiped out most of the time. Despite receiving more than five blood transfusions to restore his blood cell numbers, relief was only partial. He was soon put on Revlimid® (lenalidomide), one of three new medications for a disease notoriously lacking options. "Within a month of taking the drug my blood cell counts started coming back up," says Hodge, who hasn't had a transfusion in four years.

MDS occurs when mutated stem cells in the bone marrow produce dysfunctional blood cells called blasts, resulting in low numbers of one or more blood cell types, including red blood cells, white blood cells or platelets. ("Myelo" refers to marrow and "dysplasia" means abnormal.)

Biology of MDS

The resulting blood cell deficiencies, or cytopenias, explain the first symptoms typically seen with the disease: extreme fatigue, weakness, bruising, infections,

bleeding and fever. “I was fatigued by 11 in the morning,” recalls Hodge. “I seriously considered retiring.”

But Hodge and many others like him are now enjoying lives relieved from many of these symptoms thanks to Revlimid, Vidaza® (azacitidine) and Dacogen™ (decitabine). “These three drugs have changed the landscape of MDS treatment,” says John Bennett, MD, a long-time MDS researcher at the University of Rochester in New York and chairman of the MDS Foundation. They offer startlingly positive results in some of the patients who respond to them. In Hodge’s case, not only did his fatigue fade but so did any sign of disease. “It put me in a complete remission,” he says.

Even with successes, MDS remains an extremely difficult disease to treat for the majority of people, cautions Charles Schiffer, MD, professor of medicine and oncology at the Barbara Ann Karmanos Cancer Institute at Wayne State University School of Medicine in Detroit. MDS is usually a progressive illness, so approximately 20 percent of patients eventually develop acute myeloid leukemia (AML). For this reason, MDS was formerly classified as a preleukemia.

While the majority of doctors today consider MDS a type of cancer, some institutions, such as Stanford Comprehensive Cancer Center, still do not classify the disease as a malignancy, which can be confusing for many patients. Further research and classification of MDS is creating more of a distinction between MDS and benign blood disorders, leading to the disease being formally defined as cancer by the National Cancer Institute, World Health Organization and numerous cancer institutions and organizations. “MDS is a malignant bone marrow disorder,” says Dr. Bennett. “We need to get that out more.”

While an estimated 10,000 to 15,000 new cases of MDS are diagnosed each year in the United States, slightly more often in men, some experts estimate the number is actually much higher. “I think we really have a population of 20,000 to 25,000, and that is the tip of the iceberg,” says Dr. Bennett. “There may be another 50,000 to 100,000 elderly Americans who probably have undiagnosed MDS.” Combine the aging baby boomer population with improved diagnostics to identify MDS patients more precisely and the number of people diagnosed with MDS will inevitably increase.

## Chasing the Cause

Though the average age of MDS diagnosis is 70, the disease can strike younger people. “I was 51 when I was diagnosed,” says Robin Whittemore of Easley, South Carolina. Whittemore developed therapy-related, or secondary, MDS following breast cancer treatment she received several years prior that included Adriamycin® (doxorubicin), a drug that carries a risk of secondary cancer. Whittemore is among the approximately 20 percent of secondary MDS cases with a known cause: exposure to certain types of chemotherapy or radiation treatment for previous cancers; exposure to certain chemicals, such as benzene; and Fanconi anemia, a rare congenital disease.

While researchers know genes play a role in the majority of primary MDS cases, the cause is largely unknown. “Perhaps it may be because we live in an

environment where the bone marrow is continually being challenged over decades by radiation, occupational hazards and other influences that are poorly identified,” says Dr. Bennett. The ability of the bone marrow DNA to optimally repair itself is limited. The repair enzymes eventually age, says Dr. Bennett, leading to a situation where the next alteration is inadequately repaired and sooner or later a person ends up with a damaged blood stem cell that grows at the expense of normal cells.

MDS is actually multiple disorders wrapped up in one. After diagnosis, the International Prognostic Scoring System, developed in the late 1990s by Dr. Bennett and colleagues, helps provide a prognosis and defines four risk groups for both overall survival and AML evolution: low, intermediate-1, intermediate-2 and high risk. Survival for most people with MDS can be less than six months to more than 10 years, depending on the subtype.

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—John Bennett, MD

### Treatment Transition

The main options available to MDS patients in the past were blood transfusions, antibiotics to prevent infection and blood cell growth factors, drugs designed to jumpstart blood cell production. Today, almost all patients still receive blood transfusions, but transfusions don't provide long-term relief and repeated red blood cell transfusions often leave patients with iron-rich blood, a serious condition if left uncorrected. (The approval of Exjade® [deferasirox], the first oral drug designed to reduce iron overload, now makes the consequences of transfusion therapy less intrusive by replacing traditional infusion-based pump therapy.)

Donor stem cell transplant—currently the only curative treatment for MDS—may not be realistic for this older population. But a recent push to find less toxic yet effective treatments led to the three notable drug approvals.

Originally told she had as few as three months to live without a stem cell transplant, Whittemore entered a clinical trial for Dacogen, an intravenous drug just approved in May. “I figured it might give me more time to find a donor,” she says. This latest drug approval for MDS came after three separate trials in about 270 patients total found that blood counts completely or partially normalized in about 22 percent of Dacogen-treated patients. Whittemore was among that percentage and is now transfusion-free, receiving growth factor injections as needed to boost her blood counts. She still battles fatigue, particularly the week after treatment. “But,” she says, “compared with breast cancer chemotherapy, this treatment was a breeze.”

While she waits for a suitable donor, Whittemore, a jewelry artisan, focuses her artistic energy on creating cancer awareness designs. “I created the Second

Chance bracelet because of the second chance at life after virtually being given a death sentence.” New schedules and doses of Dacogen are now being evaluated that may be even more effective.

Other chemotherapy drugs for MDS include Vidaza and an older drug called cytosine arabinoside (ARA-C). The response rates are comparable between Dacogen, Vidaza and cytosine arabinoside, says Dr. Bennett, but the newer agents cause far fewer side effects. “Currently it’s hard to make a judgment whether one is better than the other.”

Normal cells rely on tumor suppressor genes to ensure normal cellular functioning and growth, but since many of these tumor suppressors have been silenced in MDS cells, abnormal growth occurs. Dacogen and Vidaza interfere with the DNA process that silences these crucial genes, thus restoring tumor suppressor function and normal functioning of the cell. Common side effects of both drugs include nausea, anemia and thrombocytopenia.

Although Dacogen and Vidaza are approved for all MDS types, in practice, only patients with more advanced disease typically receive these drugs. Singling out Vidaza, MDS researcher Alan List, MD, says the most striking thing is the drug’s ability to delay or suppress the development of leukemia. “Its best effects are going to be in people who are higher-risk patients for whom you have to extend survival and control the potential for leukemia evolution,” says Dr. List, division chief of malignant hematology at H. Lee Moffitt Cancer Center and Research Institute in Tampa.

The May 2004 approval of Vidaza served as fortunate timing for Ernie Widmann, a 69-year-old investment consultant from suburban Philadelphia who was diagnosed with MDS in late 2005. After five cycles of daily Vidaza treatment, Widmann’s blood counts improved to the point where his doctors took him off the drug. “They were pretty intense injections,” he recalls. “But after the first couple of treatments my numbers rebounded.” He has remained transfusion-free since his last treatment. In general, about 30 to 50 percent of patients receiving Vidaza see improvements in their blood cell counts.

Beyond the impact on DNA processes, researchers suspect an overly exuberant immune system may partly explain why the bone marrow produces abnormal blood cells in some types of MDS. Younger, low-risk patients respond particularly well to treatment aimed at weakening the immune system.

Revlimid, a once-daily oral derivative of Thalomid® (thalidomide), works by enhancing the effect of erythropoietin, the body’s regulator of red blood cells, says Dr. List. Revlimid is most effective against the subtype for which it was approved late last year—5q deletion MDS, a mild type of MDS where chromosome 5 lacks a portion of DNA. It reduces the need for transfusions in about two-thirds of patients, and eliminates the 5q deletion chromosomal abnormality in up to 75 percent of patients, including Chet Hodge. “I was astounded when I had a bone marrow sample three months after starting the drug that showed no sign of the 5q deletion,” says Hodge.

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Aerospace engineer Chet Hodge went into complete remission after taking Revlimid. Photo by Darryl Webb

In MDS patients without the 5q deletion, the results of Revlimid are not as robust, but trials show about 27 percent of patients become transfusion-free and 44 percent have some improvement in their blood cell counts. The drug's main side effects are rash, fatigue and neutropenia (low neutrophil count), a side effect managed well by growth factor treatment.

Immunosuppressive approaches under investigation for MDS (primarily low-risk MDS) include antithymocyte globulin, steroids and the antitumor necrosis factor therapies, Remicade® (infliximab) and Enbrel® (etanercept).

### Add It Up

Now with several proven agents at their disposal, researchers believe combining drugs may enhance survival and possibly suppress disease progression. Vidaza and Dacogen are already in clinical testing with various other drugs. "We're where Hodgkin's disease researchers were in the early 1970s—they had a lot of agents that worked. They had to put treatments together to improve on that," says Dr. List.

Possibly joining the next wave of MDS therapies is Telintra™ (TLK199), an oral drug that promotes blood cell growth, and farnesyl transferase inhibitors Zarnestra® (tipifarnib) and Sarasar™ (lonafarnib), which interfere with enzymes involved in activating cancer-promoting genes.

"When you get your first drug approved for a disease, it suddenly attracts interest," says Dr. List. And from that first drug has come the beginnings of a menu of MDS therapies. Experts agree it is unlikely Vidaza, Dacogen and Revlimid are the final answer in MDS treatment, but the research continues, and for Dr. List, "this is just the beginning."