Researchers have seen improvements in supportive care and the introduction of new therapies for myelodysplastic syndromes (MDSs), but the treatments remain largely supportive.

Currently available therapies benefit only a few patients with different stages of MDS, said Charles Schiffer, M.D., of the Karmanos Cancer Center at Wayne State University in Detroit. These clinical shortcomings reflect the inadequate understanding of the underlying biology of MDS. However, the development of tools for exploring the cellular and molecular biology of disease processes offers hope that a more effective therapy is possible.

Schiffer said that doctors now have tools to explain things they don’t yet understand. “Now that you can do things with old slides or paraffin, don’t throw these [resources] away,” he said at the American Society of Hematology meeting in December. “Find someone who can help you explain things.”

An abnormality of blood-forming cells in bone marrow, MDS has a checkered history as a cancer. Until recently, many oncologists did not consider MDS to be a malignancy. However, that view has changed as evidence emerged that MDS is a clonal disease, meaning that it arose from one cell, which is a characteristic of cancer. Also, about 30% of MDS cases eventually progress to acute myeloid leukemia.

Currently, stem-cell transplants offer the potential for long-term survival for MDS patients, though several types of chemotherapy have recently been approved for MDS. The immune system stimulant lenalidomide has also demonstrated considerable activity in one particular variant of MDS known as 5q-. However, supportive care and symptom relief are often the only options; the therapy may include red blood cell transfusions and growth factors for blood cells. Researchers hope that new investigational tools, such as gene array expression, will help clarify some of the unknowns surrounding MDS.

International efforts so far have done little to improve the fundamental understanding of MDS. For examples, Schiffer looked to the international prognostic scoring system for classifying MDS and developing standards to determine the disease’s response to treatment. The prognostic scoring system uses three criteria to determine the stage of MDS—the proportion of immature blood cells in the bone marrow, the presence or absence of chromosomal abnormalities, and the total blood cell count—but they do not often translate to clinical symptoms. “All of these things focus on features of the disease and not other clinical considerations in the patient,” Schiffer said.

Different information is needed to make real progress in MDS, he said. For an example he cited a German study of genetic abnormalities in more than 2,000 MDS patients presented at the 2005 hematology society meeting. The analysis showed that certain genetic changes (deletions at 5q and 20q) are associated with a favorable prognosis, while others are associated with a worse prognosis or have little effect on outcome.

“When we have more information like this, it might help us in recommending what to do—or not,” Schiffer said.

Few Options Available

While there is much uncertainty about the causes and types of MDS, considerably less ambiguity surrounds how to currently manage MDS, primarily because there are a limited number of options for treatment, Schiffer said. A sometimes-unpredictable response to treatment continues to confound physicians. Some patients do well with no treatment, whereas others with more favorable clinical characteristics do not respond to therapy. However, Schiffer said, clinicians can extract valuable information from careful observations of such patients.

Among therapies for transfusion-dependent MDS patients, few data support the effectiveness of azacytidine and decitabine, the most common treatments. Major trials of azacytidine and decitabine (two of the three chemotherapy agents approved for MDS) resulted in a 1-year overall response rates of 17%–21%. In contrast, immunosuppressive therapies have produced more encouraging results that should be explored further, Schiffer said. The best responses were seen in patients with refractory anemia. Moreover, patients who become transfusion independent after immunotherapy often have prolonged responses that can last for years.

“This is very, very different from any therapy that we administer for this disease,” Schiffer said. “We don’t understand the mechanism by which immunosuppression works, but there is absolutely no question that this phenomenon exists. It can produce durable responses. It’s not just for patients with [very low blood cell counts in their bone marrow]. I think it’s imperative for us to learn more about how this works.”

The immune modulator lenalidomide has shown activity in patients with good prognosis and who do not have the 5q deletion. In that population, lenalidomide allows about 25% to stop receiving transfusions. However, the drug does not appear to help restore neutrophils and platelets, Schiffer said.

Another treatment option for certain patients is chelation therapy, which involves giving a drug that removes excess iron that can accumulate in the blood after multiple transfusions. Chelation therapy should be reserved for patients who will probably die because of their iron overload, Schiffer said. It does not treat the underlying disease. Patients who have other substantive medical problems (such as cardiac, renal, or pulmonary disease), who are likely to progress to acute myeloid leukemia, or who have life-threateningly low blood cell counts should not be considered for chelation.

Studies Bring Hope

Although MDS has a history marked by uncertainty and disappointment, current
activities in the field offer potential leads. Ongoing clinical and epidemiologic research holds promise for clearing up some of the uncertainty surrounding MDS and for improving outcomes, according to Mikkael Sekeres, M.D., assistant professor of medicine at the Cleveland Clinic Taussig Cancer Center.

Several longitudinal studies seek to better define the epidemiology of MDS and determine more precisely its effect on patients and society. Efforts to improve risk stratification and prognostic techniques will probably give more weight to transfusion needs and move toward development of a graded scoring system for blood cell counts, Sekeres said.

Current approved drugs can’t cure MDS, but when used appropriately, they can achieve responses in most patients. The problem with a drug like lenalidomide, for example, is that it works best in a narrowly defined subset of patients with MDS.

“It works in more than two-thirds of the [10% of patients in that category] and works for a median of more than 2 years. The trick is in knowing when to give the drug to get that 2 years of life,” Sekeres said.

Three areas of future development have already begun to emerge, Sekeres continued. One focus will be on use of drug combinations and expansion of indications for approved agents. Sekeres is the principal investigator in one trial evaluating the combination of lenalidomide and azacytidine for patients with advanced MDS. A second area of therapeutic development involves use of growth factors, such as AMG 531, a peptide that stimulates platelet production. Strategies for administering and combining growth factors also will be developed and refined, Sekeres predicts. And a third area will focus on the development of new types of therapy that target specific enzymes and molecules thought to play a role in the progression of MDS.

Several studies reported at the hematology meeting provided insight into roles of existing and new therapies for MDS. A group at the University of British Columbia in Vancouver reported what they believe to be the first evidence of improved survival in MDS patients receiving chelation therapy. The median overall survival was 36 months for 18 patients who received the therapy. However, patients classified as low- or intermediate risk by a prognostic scoring system had not reached a median survival after 160 months, whereas similar-risk patients who did not receive chelation therapy had a median survival of 40 months. However, the results are preliminary and randomized studies are still needed.

Two different reports provided evidence of lenalidomide’s effectiveness in transfusion-dependent MDS patients. Among 214 patients without the 5q deletion, lenalidomide was associated with transfusion independence in 56 (26%) after a median of 5 weeks of treatment. In the smaller of two studies in patients with a 5q deletion, 24 (56%) of 43 patients had major objective responses to lenalidomide, including 20 who had prolonged periods of transfusion independence. In the larger study of 148 patients, 112 (76%) had a reduced need for red cell transfusion and 99 (67%) became transfusion independent, said Alan List, M.D., professor and chief of malignant hematology at the University of South Florida and H. Lee Moffitt Cancer Center and Research Institute in Tampa.

New therapies to treat MDS are also under investigation. Initial results with an investigational targeted therapy showed modest activity in low- and intermediate-risk patients. A small study examined the activity of a kinase inhibitor Sci-469, which blocks induction of proinflammatory, proangiogenic, and proapoptotic cytokines. Of 29 patients who could be evaluated, five had major hematologic improvement, five had minor hematologic improvement, and one had a partial response, reported Lubomir Sokol, M.D., Ph.D., an investigator in the malignant hematology division at H. Lee Moffitt Cancer Center and Research Institute.

“I think we’re going to see a lot of activity related to MDS in the near future,” Sekeres said.