14TH INTERNATIONAL SYMPOSIUM ON MYELODYSPLASTIC SYNDROMES

PATIENT SUMMARY

MAY 3–6, 2017 • VALENCIA, SPAIN
Dear Patient or Caregiver,

The purpose of this guide is to provide you with MDS related information recently presented at the MDS Foundation’s **14th International Symposium on Myelodysplastic Syndromes** that took place in Valencia, Spain from May 3 – May 6, 2017. This guide includes material related to clinical aspects of MDS diagnosis, prognosis, and management as well as the newest data in MDS basic and translational research. The main lectures were delivered by recognized international leaders but also included high-level research talks selected from the abstracts submitted by attendees. New information that researchers hope is important enough to be presented at this meeting is submitted a few months ahead of the conference in the form of an abstract – a brief summary of the study and its results – and authors of the most interesting noteworthy abstracts are asked to present their research in more detail, either in the format of a printed poster or an oral presentation.

As the 14th meeting in our **biennial MDS international symposium program**, this meeting in Spain hosted nearly 1,100 delegates and included three workshops dedicated to specific MDS-related research developments. Also included were 10 plenary scientific sessions, roundtables and debates, and an abstract poster viewing. First the first time, we also offered a pharmacists session and medical pipeline sessions.

We selected the following discussions to summarize because we feel they are the most relevant and important for patients who are currently living with MDS. Please note that some of the research results discussed in this summary may include experimental drugs that are not yet approved for general use, or investigations of potential new uses of previously approved treatments. By providing summaries of these talks, we do not intend to recommend or endorse any particular medication or treatment approach. Our goal is to simply inform you about current news and trends in research related to MDS.

If you are interested in participating in research studies such as those discussed in this guide, we encourage you to speak with your doctor about clinical trials, or call the MDSF Patient Liaison for assistance at 1-800-637-0839. Please feel free to also reach out to MDSF if you have any questions regarding these summaries or any aspect of managing your disease.

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NEW CLASSIFICATION SYSTEMS

World Health Organization’s 2016 Classification System for MDS

Dr. Ulrich Germing, M.D. (Heinrich Heine Universität Düsseldorf, Germany) gave an update on the World Health Organization (WHO) classification system for MDS. Doctors often use this system to assess MDS severity and predict a patient’s outcomes. But this system, last updated in 2008, has some weaknesses. For example, up to 20% of patients with MDS have less severe cytopenia* than the WHO’s cutoff level for an MDS diagnosis.

A panel of experts revised the WHO system in 2016 to improve its ability to predict the outcomes for individual patients. An independent analysis of data on 3,528 patients with MDS from the German MDS registry showed that the new WHO system categories work well. The main changes to the WHO 2008 classification system are described below.

1. **Category names**
   The 2016 system has changed the names of several MDS subtypes by replacing “refractory anemia” with “MDS” wherever the term “refractory anemia” appeared. For example, refractory anemia with excess blasts I and II is now MDS with excess blasts 1 and 2, respectively.

2. **New category for MDS with ring sideroblasts**
   The 2016 system redefined the old refractory anemia with ring sideroblasts and refractory cytopenia with multilineage dysplasia and ring sideroblasts subtype of MDS. The new category, MDS with ring sideroblasts, applies to patients who have single or multilineage dysplasia and one of the following (because these patients have the same favorable risk profile):
   - A least 15% of ring sideroblasts
   OR
   - At least 5% ring sideroblasts in patients with a mutation in the SF3B1 gene

3. **New definition of MDS del(5q)**
   The 2016 system defines this MDS category as:
   - Less than 5% blasts in the bone marrow

4. **More precise definitions of MDS, unclassifiable**
   This category now includes:
   - Less than 5% bone marrow blasts, no del(5q), and less than 1% blasts in peripheral blood
   - Less than 5% bone marrow blasts, no del(5q), and 1% peripheral blood blasts at two or more times
   - No clear dysplasia but abnormalities in chromosomes that are typically seen in MDS

5. **New cutoffs for the proportion of blasts in bone marrow**
   The new cutoffs are:
   - MDS with excess blasts 1: 5% to 9% blasts in bone marrow or 2% to 4% blasts in peripheral blood
   - MDS with excess blasts 2: 10% to 19% blasts in bone marrow or 5% to 19% blasts in peripheral blood

MDS Risk Assessment Based on Other Diseases in Older Patients

Dr. Fernando Ramos (Hospital Universitario de León, Spain) explained that patients with MDS often have comorbidities. Patients are almost as likely to die of their comorbidities as of MDS.

Some comorbidity indexes can be used to assess patients. Most of these tools are generic, but the MDS-Specific Comorbidity Index is now available. More research is needed on its ability to accurately predict outcomes.

The Comprehensive Geriatric Assessment evaluates many factors in elderly patients, including comorbidities, physical and mental performance, nutritional status, muscle mass, and socioeconomic status. All of these factors should be taken into account, especially given the aging of the general population in North America and Europe. But this tool has some limitations. It is time consuming to use and needs to be completed by someone with geriatric expertise. Also, the screening tools used to identify patients who need the full assessment are far from perfect.

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* Please see LIST OF ACRONYMS and GLOSSARY OF TERMS for all highlighted terms.
Some simplified geriatric assessment tools, including the Geriatric Assessment in Hematology scale, provide an alternative to the more comprehensive and generic tools. This tool measures the number of drugs the patient is taking, walking speed, mood, daily activities, perceived health status, nutrition, mental status, and comorbidities. It is currently being tested.

Another scale was developed to predict mortality at 4 years in adults older than 50 using just 12 questions. This questionnaire asks about comorbidities, behaviors, functional and physical performance, age, gender, and current smoking. Dr. Ramos tested this index in 200 patients with MDS. Use of this tool improved the ability of the revised International Prognostic Scoring System (IPSS-R) to predict patient survival. But the index didn’t improve the ability to predict risk of progression to acute myelogenous leukemia (AML).

Frailty can be defined as age-related loss of physiological capacity that can lead to loss of energy, motivation, illness, and disability. Frailty can be measured in different ways, but Dr. Ramos prefers the Clinical Frailty Scale. This scale has nine categories, ranging from very fit to terminally ill. The Clinical Frailty Scale was tested in more than 400 Canadian patients with MDS, and it did a good job of predicting overall survival independently of the IPSS-R.

Dr. Ramos believes that patients should receive the best available treatment for their MDS if their life expectancy would not otherwise be very short. He recommends taking into account IPSS-R score, age-adjusted frailty, and comorbidity for MDS prognosis.

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**CHROMOSOME AND GENETIC TESTING FOR MDS DIAGNOSIS AND PROGNOSIS**

**Uses of Chromosome Testing**
Dr. Francisco Solé (Josep Carreras Leukaemia Research Institute, Barcelona, Spain) reported that new technologies, such as next-generation sequencing (NGS), can identify gene mutations indicating the presence of genetically abnormal cells and provide information about the likely prognosis. Some experts have therefore questioned whether doctors still need to evaluate cytogenetic abnormalities in patients with MDS. Dr. Solé argued that chromosome testing is still both useful and necessary and is likely to remain so in the coming years because it has value for prognosis, diagnosis, and treatment decisions.

**Prognosis**
The original International Prognostic Scoring System (IPSS) often failed to identify patients with apparently low-risk or intermediate-risk MDS who actually had a poor prognosis. The IPSS-R considers more abnormalities in certain chromosomes and takes the severity of cytopenias into account. Overall, the IPSS-R does a better job of categorizing risk in patients with MDS than the original IPSS.

Cytogenetic testing is also useful for monitoring a patient over time. If, for example, a change happens in a patient’s chromosomes, this could affect his or her prognosis.

**Diagnosis**
Diagnosis of MDS requires laboratory testing and a bone marrow biopsy to assess the shape of blood cells, the presence of blasts, and cytogenetic abnormalities. Doctors use this information to predict patient outcomes, choose the appropriate treatment, and monitor patients over time.

No more than half of patients with MDS have abnormalities in their chromosomes. Using a combination of genomic arrays, genetic sequencing, and cytogenetic testing can identify changes in genes or chromosomes in 90% of patients. No one technique is enough—they are all complementary.

**Treatment Decisions**
Certain treatment decisions for patients with MDS are based on cytogenetic information. Specifically, lenalidomide is the recommended treatment for patients with del(5q) MDS. Similarly, azacitidine is appropriate for patients with higher risk MDS who often have aberrations in chromosome 7 or a complex karyotype.
Use of Genetic Testing

Somatic Mutations in Prognosis

Dr. Rafael Bejar (Moore Cancer Center, UC San Diego, United States) reported that somatic mutations can give doctors more information than standard laboratory tests. Researchers have identified many somatic mutations in patients with MDS.

An analysis of data from more than 3,500 patients found that those who had a somatic mutation in the SF3B1 gene alone tended to survive longer. But, several other mutated genes were associated with poorer outcomes. On average, prognosis worsened with every additional somatic mutation in genes other than SF3B1. Some of the mutations were associated with better or worse outcomes than the IPSS-R would predict.

Just looking at individual mutations in a patient doesn’t give the whole picture—it’s important to look at all mutations in each patient because this pattern can influence outcomes. For example, patients with SF3B1 mutations tend to have very few other mutations that are associated with a poor prognosis. But patients without SF3B1 mutations are likely to have mutations associated with a poor prognosis.

Somatic Mutations in Diagnosis

The expert panel that updated the WHO system didn’t choose to include additional mutations to define MDS subtypes because some people can develop mutations associated with MDS as they age, even though they have no other signs of MDS. This condition is known as Clonal Hematopoiesis of Indeterminate Potential, or CHIP. If an older patient with low blood counts has one of these mutations, it might be hard to tell if the mutation is a marker of MDS or just part of the aging process.

However, some mutations might be useful for diagnosing MDS. For example, the WHO classification system uses SF3B1 mutations to classify MDS with ring sideroblasts. Other mutations can predict progression to AML or another blood cancer in patients with unexplained cytopenias. Having no mutations in certain MDS genes means that the patient likely has a good prognosis. Mutations can also be useful for predicting prognosis once a patient’s MDS has been diagnosed.

Example: Study of Changes in Genetic Mutations for Prognosis in MDS and Secondary AML

Dr. David Sallman (H. Lee Moffit Cancer Center & Research Institute, United States) described a study that used information on genetic mutations for prognosis. This study included 157 patients with MDS, chronic myelomonocytic leukemia (CMML), or secondary AML. All patients were assessed with NGS at least twice.

The most common mutations at the first NGS test performed before treatment were in ASXL1, TET2, and DNMT3A. On average, patients had two mutations at this time. By the second assessment, conducted after patients were treated, 13% of patients had lost all their mutations, 27% had lost one mutation, and 37% had gained a mutation. Over half had increases in variant allele frequency.

Patients treated with azacitidine or decitabine who were in complete remission had decreases in variant allele frequency, although this change was not statistically significant. But patients who had the same treatments and were not in complete remission tended to have an increase in variant allele frequency. The results were similar for patients treated with chemotherapy. Most patients who had had a stem cell transplant and were in complete remission had no MDS mutations. But all those tested after a relapse had developed mutations. Most patients who had no mutations detected by the first NGS were alive 18 months later, compared with only 34% of those with mutations at the first NGS. Those who lost their mutations at the second NGS survived much longer than those who continued to have mutations.

No particular type of mutation predicted whether a patient would have no mutations after treatment. However, most patients who had a mutation in the TP53 gene lost this mutation after treatment with azacitidine or decitabine. Mutation gains and increases in variant allele frequency did not predict overall survival. Loss of mutations did predict better outcomes, but when patients who lost all mutations were excluded from the analysis, loss of mutations had no association with better outcomes.

The results from this study highlight the prognostic value of repeating NGS. They also show that negative NGS results after treatment indicate a good prognosis for patients with MDS.
Early Decreases in Platelet Counts for Prognosis of Lower-Risk MDS

Dr. Raphael Itzykson (Hôpital Saint-Louis, Université Paris Diderot, France) described the results of a study that assessed early declines in platelet counts for prognosis of lower-risk MDS using data from the European MDS Registry. The study included 807 patients from Europe and Israel who had been diagnosed within the previous 100 days. All patients had platelet count information when they joined the registry and again about 6 months later. About 60% were male, the median age was 73 years, and 70% had very low-risk or low-risk MDS according to the IPSS-R.

During the first 6 months after diagnosis, platelet and neutrophil counts dropped by 5%, on average. Also, 27% of patients had rapid declines of at least 20% in platelet counts. The most striking difference between patients whose platelet counts did and didn’t drop by at least 20% was the frequency of red blood cell transfusions at inclusion in the registry and 6 months later.

Patients with a rapid platelet decline tended to survive for a median of 33 months, while those with slower declines survived a median of 57 months. This link between a rapid drop in platelet count and shorter survival held for patients in all IPSS-R categories, except for those with very low-risk MDS. In addition, needing blood transfusions at the 6-month assessment was independently tied to shorter survival.

Dr. Itzykson concluded that a 20% or greater drop in platelets over the first 6 months after diagnosis is associated with a poor prognosis in patients with “lower-risk” MDS. Evaluating changes in platelet counts and need for red blood cell transfusions at 6 months could be a free and reliable way to determine prognosis in MDS.

PREDICTING TREATMENT RESPONSE

Predicting Outcomes of Erythropoiesis-Stimulating Agents and Lenalidomide in Low-Risk MDS

Erythropoiesis-stimulating agents (ESAs) increase red blood cell counts in up to 70% of patients with low-risk MDS who have anemia. About 10% of patients with MDS have del(5q) MDS, and lenalidomide is the best treatment. Dr. María Díez Campelo (Universitario de Salamanca, Spain) described some of the factors that doctors can use to predict the effects of these treatments.

Erythropoiesis-Stimulating Agents

The factors that predict responses to ESAs include:

- Hemoglobin level higher than 10 g/dl
- No blasts in blood or bone marrow
- Few if any abnormalities in chromosomes
- Low-risk or very-low-risk MDS according to the IPSS or IPSS-R
- Higher ESA doses
- Need for few, if any, red blood cell transfusions
- Erythropoietin level lower than 200 U/L

Lenalidomide in Del(5q) MDS

Almost 65% of patients stop needing regular red blood cell transfusions with lenalidomide. Their hemoglobin levels rise, which is important for longer responses and better quality of life.

Perhaps the most important predictor of response to lenalidomide is a higher platelet count. Patients are also more likely to respond if they don’t need many transfused red blood cell units, were diagnosed with MDS in the past 2 years, and don’t have many cytogenetic abnormalities.

Patients with a mutation in the TP53 gene or strong expression of p53 are less likely to achieve cytogenetic remission after lenalidomide treatment. Mutations in U2AF1 and DDX41 genes and expression of CRBN and CSNK1A1 might also lower a patient’s chances of responding to lenalidomide.
Lenalidomide in Non-Del(5q) MDS

Lenalidomide is only effective at durably eliminating the need for regular red blood cell transfusions in a small proportion of patients (17% according to one study) with non-del(5q) MDS. Response rates are highest in patients who

- Are female
- Need less than four units of transfused red blood cells/month
- Have had MDS for less time
- Have a platelet count higher than 150 x10^9/L
- Have a favorable type of MDS according to the WHO classification system
- Have been treated with ESAs in the past
- Are treated with 10 mg/day of lenalidomide (as opposed to 5 mg/day)
- Have low-risk MDS
- Do not have many chromosome abnormalities or any linked with a poor prognosis

Predicting Outcomes of Azacitidine Treatment

Dr. Raphael Itzykson, (Université Paris Diderot, France) discussed markers of hypomethylating agent (HMA) response. Whether these drugs are equally effective in all types of higher-risk MDS is a tricky question to answer. They don’t cure MDS, and response rates are not useful measures of their effectiveness.

One potential marker of HMA response and effects on survival is a doubling of the platelet count after one cycle of HMAs. But this happens in only a small proportion of patients. Also, patients with increased platelet counts don’t necessarily do well over the long term.

The usual markers used to predict whether a given patient will respond to HMA treatment don’t work well. For example, although some evidence shows that older patients and those with comorbidities don’t do as well with HMAs, this evidence has some important weaknesses. Abnormalities in chromosomes at the start of treatment also do a poor job of predicting responses to HMAs.

According to Dr. Pierre Fenaux (Hôpital St. Louis/Université Paris 7, France), the factors that seem to be most useful for predicting HMA outcomes include chromosome abnormalities, IPSS-R score, and mutations in certain genes. Dr. Itzykson reported that experts have combined different types of markers into prognostic scoring systems. He worked on one of these systems, which categorizes MDS as low, intermediate, and high risk based on how long patients are likely to survive with azacitidine treatment.

Researchers are also exploring whether genes involved in faulty DNA methylation might be useful for predicting HMA outcomes in patients with MDS.

Several ongoing efforts, including the HARMONY study, have a good chance of identifying the factors that predict HMA outcomes in MDS and other blood cancers and of predicting the effects of HMA treatment on quality of life, healthcare costs, and care strategies.
Dr. Aristoteles Giagounidis (Marian Hospital Düsseldorf, Germany), reported that some patients with del(5q) MDS who have a complete cytogenetic remission may enjoy long periods of transfusion independence after lenalidomide is discontinued. This is especially true if they were treated with lenalidomide for at least 6 months. But some have a relapse years later.

If MDS doesn’t progress after a patient stops responding to lenalidomide, the patient might respond to lenalidomide again after a “drug holiday,” at least for a while. But if MDS does progress during lenalidomide treatment, the prognosis is poor.

Patients who never respond to lenalidomide only survive for about 18 months, on average. The risk of progression to AML increases steadily over time after lenalidomide failure.

L-leucine, an amino acid, is effective for anemia in experimental mice with del(5q) MDS and in people with Diamond-Blackfan anemia. Clinical trials are testing L-leucine in patients with del(5q) MDS after lenalidomide failure.

Many patients do well with stem cell transplantation after lenalidomide failure. Even patients whose MDS progresses during lenalidomide treatment can benefit from this procedure. HMA s can prolong survival in patients who aren’t eligible for stem cell transplantation.

The options after lenalidomide failure for patients with del(5q) MDS are to stop the lenalidomide temporarily and start it again, use HMA s if the MDS progresses, and offer stem cell transplantation to eligible patients (especially those who are younger). Two experimental treatments, L-leucine and cenersen, might become options after more research.

Enasidenib, an Inhibitor of the Mutant IDH2 Gene, in MDS after Treatment Failure

Dr. Eytan Stein (Memorial Sloan Kettering Cancer Center, New York) reported that about 5% of patients with MDS have a mutation in the IDH2 gene. This mutation leads to the accumulation and release of R-2-hydroxyglutarate, a substance that affects DNA methylation.

Enasidenib is a drug that inhibits mutant IDH2. A phase I/II clinical trial of enasidenib in 239 patients with AML included 17 patients with intermediate-1, intermediate-2, or high-risk MDS. All patients had an IDH2 mutation and had experienced treatment failure. The median age was 67 years, and 71% were male.

Ten of the 17 patients with MDS responded, including 1 with a complete remission, 1 with a partial remission, 1 with a complete response in the bone marrow, and 5 with higher blood cell counts. In addition, 7 of the 13 who had been treated with HMA s in the past responded. The most serious side effects included hyperbilirubinemia (jaundice), pneumonia, platelet shortages, and anemia. No patients died from the treatment.

Most patients who responded left the study because they had a stem cell transplant, their disease progressed, or they died. But a few patients stayed on the study for more than a year. The survival rate at 1 year was 58%.

Dr. Ades noted that the European IDEAL study will provide more information on enasidenib in patients with MDS who have an IDH2 mutation and have not responded to HMA s.
NOVEL TREATMENTS AND COMBINATIONS OF TREATMENTS

The Best Partner for HMA in Higher-Risk MDS

Dr. Mikkael Sekeres (Cleveland Clinic, Ohio) focused his presentation on combinations of HMAAs and other drugs for higher-risk MDS.

A study compared azacitidine alone to the combination of azacitidine with the histone deacetylase (HDAC) inhibitor entinostat in patients with higher-risk MDS, CMML, or AML. Results were negative because the combination treatment group had higher rates of low platelet counts and fatigue. Results were also disappointing for the combination of azacitidine with the HDAC inhibitor pracinostat because patients in the placebo group did better than those in the treatment group.

But the combination of azacitidine and vorinostat seemed more promising. In a phase II clinical trial, about 70% of patients with untreated higher-risk MDS, CMML, or AML responded to the treatment, which was about double the expected rate for azacitidine alone. These responses lasted an average of 16 months. Similarly, response rates and duration of response were promising in a phase I-II clinical trial of the combination of lenalidomide and azacitidine for higher-risk MDS.

These findings led to a larger randomized phase II clinical trial in 282 patients with higher-risk MDS or CMML. The study treatments were azacitidine alone, azacitidine and lenalidomide, or azacitidine and vorinostat. The average age of study participants was 70 years. Unfortunately, response and survival rates were not significantly different between the three groups. Also, more patients in the two combination arms needed dose reductions or left the study because of complications than in the azacitidine-only arm.

Dr. Fenaux added that studies are also evaluating combinations of azacitidine with other treatments, such as valproic acid, venetoclax, immune checkpoint inhibitors, and idarubicin for higher-risk MDS or CMML. Other research is assessing more intensive HMA treatments or lower doses for longer use. Studies are testing different drugs, including venetoclax, cenersen, and a 10-day decitabine cycle, for MDS with TP53 mutations.

Dr. Sekeres concluded that azacitidine alone is still the standard treatment for higher-risk MDS. But some evidence hints at better and more long-lasting responses for combination treatments if patients stay on them long enough. The HMA “partners” under investigation might become options for higher-risk MDS in some patients.

Combination of Eltrombopag and Azacitidine for MDS with Low Platelet Counts

Dr. Michael Dickinson (Peter MacCallum Cancer Centre, Melbourne, Australia) explained that low platelet counts are common in patients with MDS, especially if they have higher-risk MDS. HMA treatment can lower platelet counts even more, especially at first, so patients often need platelet transfusions and lower HMA doses. Effective treatment for low platelet counts can reduce the patient’s need for platelet transfusions and bleeding risk while allowing the patient to get the most effective HMA doses. But treatment options for severe platelet shortages in high-risk MDS are limited.

SUPPORT was a phase III clinical trial that compared eltrombopag plus azacitidine to placebo plus azacitidine in 356 patients with a low platelet count. The study measured the proportion of patients who did not receive platelet transfusions during the first four cycles of azacitidine. On average, patients were 68 years old, and 39% were female. Most patients had intermediate-2 or high-risk MDS according to the IPSS, and most did not need regular platelet transfusions.

An independent committee recommended ending the study early when the combination treatment arm had been treated for a median of 83 days and the placebo arm had been treated for 149 days. The reason was that only 16% of patients in the combination arm were platelet transfusion independent during the first four cycles of azacitidine. On average, patients were 68 years old, and 39% were female. Most patients had intermediate-2 or high-risk MDS according to the IPSS, and most did not need regular platelet transfusions.

At the final assessment of the 356 patients, only 16% of the combination treatment arm achieved transfusion independence, compared with 31% in the placebo arm. Rates of survival, side effects, and disease progression were the same in the two arms. But the rates of serious side effects and treatment discontinuation were higher in the eltrombopag arm.
A third of patients have needed their doses lowered because of low blood cell counts. At this time, 64% of 56 patients who could be evaluated have responded, including 27% with a complete response. On average, responses last for six treatment cycles. Detected chromosome abnormalities disappeared in 24% of the 21 patients who had these abnormalities. Patients have survived a median of 14 months. The only factor found to be associated with worse survival is having several chromosome abnormalities.

Twenty-one patients are still enrolled in the study. Of these patients, seven still have a complete response, seven have a response in their bone marrow, five haven’t yet responded, and two are finishing their first treatment cycle. Forty patients have been taken off the study because of disease progression, AML, lack of response, stem cell transplantation, or death.

A phase III clinical trial is evaluating guadecitabine for higher-risk MDS after HMA failure.

Guadecitabine for Untreated Higher-Risk MDS or CMML

Dr. Guillermo Montalbán-Bravo (M.D. Anderson Cancer Center, Houston, Texas) stated that, on average, patients with higher-risk MDS treated with HMAs survive, on average for only 4–6 months, so they need new treatments. Previous research has shown that guadecitabine, a form of the HMA decitabine that resists metabolism, is safe and effective in MDS and CMML, even in patients who have been treated with other HMAs in the past.

A phase II clinical trial of guadecitabine in patients with untreated intermediate-2-risk MDS, high-risk MDS, or CMML is measuring overall response rates and survival. Patients are treated with guadecitabine over 5 consecutive days every 28 days. So far, the study has enrolled 61 patients, including 53 with MDS. Their median age is 69 years, and 64% are male.

About 85% of patients have had at least one side effect, usually fatigue, nausea, fever, or infections. Four patients have died of cardiac arrest, septic shock, or pneumonia.

Ongoing Clinical Trials in Europe and the United States

Dr. Lionel Adès (Hôpital Saint Louis, Paris Diderot University) described recent and ongoing MDS clinical trials in Europe, and Dr. Guillermo Garcia-Manero (M.D. Anderson Cancer Center, Houston, Texas) discussed trials based in the United States. Because MDS has very different features in different patients, no one drug can cure most cases of MDS.

Low-Risk MDS

Phase II clinical trials in Europe have shown that two experimental drugs, sotatercept and luspatercept, might be effective for anemia for patients with low-risk MDS who don’t respond to ESAs. They work at a later stage of red cell maturation than ESAs. In these studies, about half the patients responded to the drugs. But the response rate was higher, at around 60–70%, in those with a mutation in the SF3B1 gene or who had ring sideroblasts.

Lenalidomide has approval for del(5q) MDS in patients who need regular red blood cell transfusions. The ongoing SINTRA-REV study in Europe is investigating whether earlier use of lenalidomide might improve responses and prevent low-risk del(5q) MDS in patients who are transfusion independent from progressing. The MEDALIST trial is a large international phase III study comparing rates of transfusion independence (lasting at least 8 weeks) with luspatercept versus placebo in patients with low-risk MDS who are transfusion dependent, have not responded to ESAs, and have ring sideroblasts.

In the United States, studies are focusing on new HMA forms that patients can take by mouth as alternatives to current forms that are infused into the patient’s vein or given under the skin. A challenge is that the cytidine deaminase enzyme rapidly clears these oral drugs from the bloodstream.
A recent U.S. phase I clinical trial assessed a combination of decitabine taken by mouth in combination with a new drug, E7727, that inhibits cytidine deaminase. The drug levels achieved with the oral formulation and degree of DNA methylation reduction were similar to those in previous studies with intravenous decitabine. A phase I/II study in the United States is now comparing an oral form of decitabine to intravenous decitabine.

Other U.S.-based research is evaluating lower doses of HMA for low-risk MDS. A phase II clinical trial compared low doses of decitabine and azacitidine in 113 patients with low-risk or intermediate-1-risk MDS. More than a third of patients in each group had a complete response, although more patients in the decitabine group had some type of response. Both drugs were tolerable. Another U.S. study is assessing shorter azacitidine and decitabine dosing schedules for low-risk MDS.

Research is also seeking treatment options for patients who experience HMA treatment failure. They might benefit from early stem cell transplantation, and Dr. Garcia-Manero is designing a study to examine this possibility.

High-Risk MDS

HMA are standard treatment for high-risk MDS. Several non-randomized phase II clinical trials have had promising results for combinations of HMA with other drugs. However, randomized trials have found that adding vorinostat, lenalidomide, or pracinostat to HMA does not increase survival. An ongoing trial in France is comparing combinations of azacitidine with valproic acid, lenalidomide, or idarubicin to azacitidine alone.

Many phase I and phase II clinical trials are evaluating a wide range of treatments, either alone or in combination with HMA, for high-risk MDS. Even though non-randomized trials have shown what appear to be “better than expected” response rates, only randomized studies will truly determine whether these responses are reproducible and translate into longer survival. A randomized phase II clinical trial in Europe is using a “pick a winner” design to quickly evaluate different combinations of drugs with azacitidine for high-risk MDS.

U.S. trials are assessing the following treatments for high-risk MDS:

- Chemotherapy for some patients, such as those with certain gene or chromosome abnormalities
- Inhibitors of molecules attached to immune cells that tumor cells can use to protect themselves from the immune system
- Inhibitors of the FLT3 gene, which promotes cell growth

Options after HMA Failure

A major challenge in treating higher-risk MDS is that many patients eventually stop responding to HMA. Many new drugs are being studied, alone or in combination with azacitidine, in the United States. Although a phase III clinical trial of rigosertib had negative results for higher-risk MDS after HMA failure, the drug lengthened survival in some patients. A Phase 3 trial, the INSPIRE study is evaluating this drug in the types of patients who benefited in the first trial, and research is also assessing different or more powerful HMA for use after treatment failure. Dr. Adès noted that the SAMBA trial in Europe is assessing talacotuzumab, a drug that attacks leukemia stem cells, in patients with MDS or AML who haven’t responded to
Improving Outcomes for Patients with High-Risk MDS

Options for patients with a TP53 mutation can include scheduling the transplantation at an earlier disease stage, using different treatments to suppress the patient’s immune system before transplantation, or using treatments that could prevent recurrence after transplantation.

According to Dr. David Valcarcel (Hospital Vall d’Hebron, Barcelona, Spain), about 70% of transplantation outcomes can be explained by patient age, overall health status, and ability to perform routine tasks. Doctors need to look at these factors closely when choosing a conditioning treatment. The best approach might be to use standard conditioning treatment in patients with high-risk MDS who are fit enough, including patients with a TP53 mutation, and to use reduced-intensity conditioning in those older than 65 who have comorbidities.

Dr. Fenaux added that patients with high-risk MDS do best with transplantation if all 10 of their donor’s blood markers match their own markers. Patients also have a better prognosis if they don’t have many cytogenetic abnormalities or mutations in certain genes. Several teams of researchers are studying treatments to prevent relapse after transplantation in patients with a high risk of relapse.

Stem Cell Transplantation Candidates

Dr. De Witte explained that stem cell transplantation is appropriate for patients with higher-risk MDS who are in otherwise good health and have a suitable donor. Stem cell transplantation isn’t a good option for patients with lower-risk MDS who have many chromosome abnormalities, persistent increases in blasts, or life-threatening blood cell shortages. Those who need at least two transfused red blood cell units a month for 6 months are also poor candidates.

The use of haploidentical stem cell transplants from family members is increasing in Europe. Most patients have acute leukemia, but 12% have MDS or myeloproliferative neoplasms. The average patient age, currently around 55 years, is rising.

Stem cell transplantation is the first choice for patients with intermediate-2-risk or high-risk MDS according to the IPSS, unless the patient has another disease or condition or the disease hasn’t responded to other treatments. The procedure is also an option for patients with intermediate-1-risk MDS who are younger, have several chromosome abnormalities or life-threatening blood cell shortages, or have progressive MDS. For patients with low-risk MDS, stem cell transplantation is recommended if they have factors associated with a poor prognosis, such as lack of response to ESAs and/or lenalidomide.

Dr. De Witte demonstrated a new online tool in development for patients with MDS and their doctors. This tool helps users figure out whether a particular patient...
is a good candidate for transplantation based on the IPSS-R. If so, the tool helps doctors choose the conditioning treatment to prepare the patient for transplantation and the donor. The tool also offers recommendations for monitoring and treatment after the procedure.

Preventing Relapse After Transplantation

Dr. Charles Craddock (Queen Elizabeth Hospital and University of Birmingham, United Kingdom) stated that relapse, which is most common in the first year after transplantation, is the major cause of stem cell transplantation failure in patients with MDS or AML. Survival rates are low after relapse, so patients who have a relapse need new treatment options.

Minimal Residual Disease and Other Predictors of Relapse

Minimal residual disease status is an important predictor of relapse in patients who have had a stem cell transplant. A better understanding is needed of the association between minimal residual disease and relapse risk to help doctors figure out whether certain patients would benefit from more treatment before or after stem cell transplantation to prevent relapse.

The FIGARO clinical trial showed that treatment before transplantation with a combination of fludarabine, cytarabine, amsacrine, busulphan, and antithymocyte globulin prolonged survival in older patients with secondary AML. These patients had a high risk of relapse because of persistent or rising levels of minimal residual disease before transplantation.

Dr. Della Porta stated that IPSS category and disease status at the time of transplantation are the most important predictors of disease relapse after transplantation. But the IPSS and IPSS-R are less useful in the 60% of patients who have no chromosome abnormalities until later in the course of their disease. Furthermore, patients with somatic mutations in the TP53 gene are more likely to have a relapse after transplantation. Adding information on mutations to the IPSS-R could improve the ability to predict the procedure’s outcomes.

Graft-versus-Leukemia Effect

Another important way to prevent relapse is to harness the graft-versus-leukemia effect. It’s possible that in some patients with MDS who have an early relapse, the donated T cells haven’t had time to attack enough of the leukemia cells. Researchers are exploring ways to accelerate the graft-versus-leukemia effect or give it more time to work. For example, an infusion of immune cells from the original donor’s blood can eliminate any remaining cancer cells. Donor lymphocyte infusions in patients with AML within the first 6 months after transplantation increase the risk of graft-versus-host disease. But they are much safer when administered at a later stage.

Other Treatments

Other treatments being studied include the targeted chemotherapy drug sorafenib for patients with a mutation in the FLT3 gene. In a retrospective analysis of 81 patients, including 26 treated with sorafenib after stem cell transplantation, the relapse rate was 8% compared with 38% in patients not treated with sorafenib. This exciting result needs to be tested in prospective studies, and some are underway.

A maintenance approach after transplantation uses low doses of HMA. Of 37 patients treated with a low dose of azacitidine starting a median of 54 days after transplantation, 16 had a relapse at a median of 8 months after transplantation. However, patients who had a CD8+ T-cell response in their immune system had a lower rate of relapse. In another study, 53% of 30 patients treated with decitabine combined with fludarabine and radiation were still alive after 443 days of follow-up, and 27% had a relapse. These studies show that HMA might be useful after transplantation in some patients. However, the results from these small studies need to be confirmed in larger studies.

Dr. Valcarcel pointed out that more intensive conditioning treatments can sometimes reduce the risk of relapse after transplantation. In addition, less intensive conditioning (also known as reduced-intensity conditioning) reduces the risk of death in patients with MDS after transplantation due to causes other than relapse, but the relapse rates are higher. Lower doses of conditioning treatment seem to benefit patients who are otherwise healthy or have few chromosome abnormalities.

New Sources of Stem Cells

Dr. Valcarcel explained that in recent years, the use of matched, unrelated donors for stem cell transplantation has increased. An analysis of data on 7,048 patients undergoing stem cell transplantation for MDS between
2004 and 2014 showed that the chance of surviving for at least 3 years was 53% in patients with early-stage MDS who had a matched related donor and 49% in those with a matched unrelated donor. Among patients with advanced MDS, the survival rates were 45% for matched related donors and 40% for matched unrelated donors. Based on these data, well-matched related and unrelated donors can be good options for patients with MDS needing stem cell transplantation.

Only a few studies have assessed umbilical cord blood as a source of stem cells in MDS. One study found that survival rates without relapse were good. However, these patients were much younger than most patients with MDS. In another study of cord blood transplantation in patients with MDS with a median age of 57 years, only 30% survived for at least 5 years, whereas survival rates were 43–50% in those with a peripheral blood transplant. The conditioning treatments were different in the two groups of patients, which might have influenced the outcomes.

Results of haploidentical donor transplants in leukemia are similar to those of transplants from related or unrelated donors. One of the few studies that included patients with MDS found poorer results with haploidentical transplantation, but another very small study found good survival rates.

Dr. Valcarel recommended that doctors consider haploidentical unrelated donors, mismatched family or unrelated donors, or umbilical cord stem cell sources for patients who don’t have a matched related donor. No one type of donor is best for all patients, but most patients have more than one potential donor.

**Stem Cell Transplantation for Older Patients with MDS**

Dr. Hidehiro Itonaga (Nagasaki University, Japan) explained that progress in transplantation approaches has increased opportunities for elderly patients to benefit from this treatment.

Dr. Itonaga reported the results of a retrospective Japanese study on a transplantation approach for older patients with MDS. This study used Japanese registry data on 651 patients with newly diagnosed MDS. Patients were 60–69 years old and had their first stem cell transplant between 2002 and 2013. Of these patients, 152 had early-stage MDS and 499 had late-stage MDS. The transplanted cells came from matched or unmatched related donors, unrelated donors, or cord blood from unrelated donors.

In the early-stage MDS group, 46% were still alive 3 years after transplantation. Rates of death due to MDS, death due to the transplant, and overall death were similar among patients aged 60–64 and those aged 65–69 years. The survival rate was lowest, at 36%, for those who received a cord blood donation. Conditioning treatment intensity didn’t affect their likelihood of surviving for at least 3 years. But patients with a lower level of functioning tended not to survive as long as patients who were better able to perform routine tasks.

Of patients with advanced MDS, 37% were still alive 3 years later. As with the patients with early-stage MDS, rates of death due to MDS, due to the transplant, and overall were similar among patients aged 60–64 and those aged 65–69 years. Survival was best in patients with a matched related or matched unrelated donor and worst in those whose transplant came from cord blood or a mismatched donor. Again, conditioning treatment intensity didn’t affect patients’ likelihood of surviving for at least 3 years. Patients with more chromosome abnormalities had a lower risk of surviving for at least 3 years, as did those who had more difficulty with daily tasks.

Dr. Itonaga believes that stem cell transplantation is a promising option for long-term remissions in older patients with MDS. The ages of 60–69 don’t seem to be a limiting factor for this procedure. But more careful management—such as choosing the right type of stem cell source and conditioning regimen for each patient as well as choosing patients with good performance status (level of functioning)—is necessary to improve outcomes after transplantation.

**Graft-versus-Host Disease and High-Risk Gene Mutations after Stem Cell Transplantation**

According to Dr. Juan Carlos Caballero (Universidad de Salamanca, Spain), somatic mutations in certain genes affect survival, risk of relapse, and response to HMA treatment. They can also predict poorer outcomes after stem cell transplantation.

Patients sometimes develop chronic GVHD after stem cell transplantation. Chronic GVHD is associated with a lower
risk of relapse, but patients sometimes develop serious health problems and can even die of this complication. Dr. Caballero summarized the findings of a study on the impact of certain somatic mutations and chronic GVHD on outcomes after stem cell transplantation. This retrospective study included 115 patients with MDS treated at five hospitals in Spain between 1998 and 2015. The median age was 53 years, and 60% of patients were male. Half had high-risk or very-high-risk MDS according to the IPSS-R. In addition, 38% had no mutations in the tested genes, one quarter had one mutated gene, another third had mutations in two or three genes, and the rest had mutations in four to six genes. Altogether, 48% survived for at least 6 years. Patients with mutations in more genes tended to have worse outcomes, but this difference wasn’t statistically significant. When the investigators divided the patients into two groups based on numbers of mutated genes, those with no more than two mutated genes had significantly longer survival and longer survival without a relapse.

Patients who developed GVHD survived longer, even if they had more than two mutated genes. Factors associated with shorter survival were having more chromosome abnormalities and mutations in TET2. Relapse rates in patients with the TET2 mutation who developed chronic GVHD were similar to relapse rates in patients without the mutation.

The results show that the number of mutations could be useful for the prognosis of MDS after stem cell transplantation. In addition, chronic GVHD may help overcome the negative impact of certain types and/or numbers of somatic mutations in patients with MDS after

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NEW TREATMENTS FOR LOW BLOOD CELL COUNTS IN MDS

Epoetin Alfa Treatment for Anemia in Lower-Risk MDS

Dr. Fenaux explained that although ESAs are commonly used to treat anemia in patients with lower-risk MDS, they have only recently been formally tested in patients with MDS in randomized, placebo controlled trials.

A phase III clinical trial compared the safety and efficacy of epoetin alfa, an ESA, to placebo in patients who had anemia and MDS. Epoetin alfa had not been approved for anemia in MDS in any country at the time of this study. On average, the 130 participants were 74 years old. Slightly more than half were male, and all had low-risk or intermediate-1-risk MDS according to the IPSS. The study’s primary endpoint was erythroid response.

During the first 24 weeks, 32% of patients treated with epoetin alfa in the study had an erythroid response, compared with 4% of those treated with placebo. Half of those who did not need transfusions at the start of the study responded, compared with 23% of those who did need transfusions. When only patients who were treated according to the study protocol were analyzed, 67% who were transfusion independent and 25% who were transfusion dependent responded.

But the study ran into some problems. The investigators had to interrupt treatment when the hemoglobin level reached 12 g/dL, so many patients could not be classified as responders because they did not reach the target by 8 weeks. Also, the evaluation of transfusion needs before treatment was based on only 8 weeks, so those who needed transfusions outside that period had to have an increase of 1.5 g/dL in their hemoglobin to be considered responders. If their baseline hemoglobin was high at the start of the study because of a recent transfusion, it was difficult to raise their hemoglobin level by 1.5 g/dL. Finally, hemoglobin levels were evaluated with different instruments that could have given different results.

The investigators therefore applied different criteria to the results, such as measuring baseline hemoglobin before transfusion and defining response as a 1.5 gram hemoglobin increase for less than 8 weeks if the drug was stopped because the hemoglobin level was higher than the target level. Finally, the reviewers evaluated responses using centrally measured hemoglobin levels. Based on these revised criteria, 46% of all patients responded to the treatment. These observations led to an ongoing effort within the MDS research community to revise the MDS International Working Group’s 2006 criterion for erythroid response.
The European Union’s regulatory agency approved epoetin alfa for anemia in MDS based on this study. This was the first approval for an ESA for this purpose anywhere in the world.

Dr. Fenaux added in a separate presentation that early treatment with ESAs in patients with low-risk MDS might delay the need for red blood cell transfusions. A randomized clinical trial will compare the effects of early versus late ESA treatment in lower-risk MDS. Another trial is assessing the ability of lenalidomide to delay red blood cell transfusions for anemia in lower-risk del(5q) MDS.

**Modified Activin Receptors: A New Treatment for Anemia in MDS**

Dr. Uwe Platzbecker (Medizinische Klinik und Poliklinik I Medizinische Fakultät Carl Gustav Carus, Dresden, Germany) described anemia as a hallmark of MDS, especially in patients who need red blood cell transfusions. Often, their immature red blood cells don’t mature normally.

Luspatercept is an experimental drug that increases red blood cell counts and hemoglobin levels by blocking the activity of cytokines that play a role in red blood cell formation. The PACE-MDS study was a phase II study of luspatercept in Germany in patients with anemia and low-risk or intermediate-1-risk MDS according to the IPSS. These patients were given luspatercept by subcutaneous injection every 3 weeks for 3 months.

In the first 15 patients treated, the drug increased hemoglobin levels in those who were transfusion independent. In addition, the number of red blood cell units transfused dropped by at least 50% in 4 of 10 patients who had needed at least four units of transfused red blood cells in the 8 weeks before the study. None of the patients had any serious side effects related to the treatment. Responses were best in patients with ring sideroblasts and/or mutations in SF3B1.

The phase II PACE extension study is following 52 patients for 5 years and is enrolling new groups that have not been treated with ESAs in the past and do or do not have ring sideroblasts. About half the patients who have responded to luspatercept. Again, response rates were highest (55–60%) in those with ring sideroblasts and/or mutations in the SF3B1 gene as well as patients with baseline erythropoietin levels that were lower than 500 IU/L.

Encouragingly, even patients without ring sideroblasts responded to luspatercept, although the number of patients without ring sideroblasts in the study is still small.

The MEDALIST trial is comparing luspatercept with placebo in patients who have MDS with ring sideroblasts, are red blood cell transfusion dependent, and are no longer candidates for ESAs. The study has completed accrual ahead of schedule, and the investigators are analyzing the trial results.

Hopefully, in the near future, another drug will be available to treat lower-risk MDS in patients who have ring sideroblasts, are transfusion dependent, and have experienced ESA failure.

**Treatment for Low Platelet Counts in MDS**

Dr. Valeria Santini (Università di Firenze, Italy) reported that about a third of patients with MDS develop thrombocytopenia, which increases bleeding risk. This effect is more common in patients with higher-risk MDS. But the percentage of patients who die of thrombocytopenia doesn’t differ by IPSS-R category. In low-risk MDS, in particular, platelet count is important for prognosis.

Patients with MDS who have mutations in the TP53 gene have lower platelet counts and worse outcomes. Dr. Santini recommended that doctors pay attention to platelet counts in these patients.

Low platelet counts sometimes respond to corticosteroids, high doses of androgens, or removal of the spleen. But these responses are often temporary and only partial.

Treatment with interleukin-1 and interleukin-11 or with human thrombopoietin and a growth factor to stimulate platelet growth is either not effective or has major side effects. HMA’s might be helpful, but they are not approved for this indication in Europe.

**Thrombopoietin Mimetic Drugs**

Thrombopoietin mimetic drugs increase platelet counts. The two available thrombopoietin mimetic drugs are eltrombopag and romiplostim. A clinical trial showed that eltrombopag increased platelet counts in patients with higher-risk MDS or AML. The treatment seemed to prolong survival, but the difference between the eltrombopag and placebo groups wasn’t statistically significant. The SUPPORT trial, which assessed the combination of
eltrombopag and azacitidine, was stopped early because of high rates of progression to AML in the treatment group and concerns about the drug’s safety. In addition, more patients in the placebo group required fewer platelet transfusions. Further studies are aimed at understanding this unexpected result.

Furthermore, a study of romiplostim was stopped early because treated patients had higher numbers of blasts, or abnormal immature blood cells. But platelet counts did rise in treated patients, they needed fewer platelet transfusions, and they had less bleeding. Dr. Hagop Kantarjian (M.D. Anderson Cancer Center, Houston, Texas) presented updated long-term results from this trial at the meeting showing that the overall survival and risks of leukemia were not different between the placebo group or those treated with romiplostim. Results from an ongoing study will provide more information on this drug.

In 40 patients with low-risk or intermediate-risk MDS, the combination of romiplostim and azacitidine raised platelet counts. In a phase II clinical trial in 29 patients with intermediate-2 MDS according to the IPSS, this combination increased platelet counts and reduced platelet transfusions compared to placebo. Only two of these patients developed AML.

Dr. Santini concluded that both eltrombopag and romiplostim increase platelet counts in MDS with severe thrombocytopenia. These drugs can also have other beneficial effects, like raising counts of other blood cells in some patients. The increase in abnormal, immature blood cells with romiplostim in lower-risk MDS seems to be temporary and reversible when the drug is stopped.

What’s New in Iron Overload Treatment for MDS?

Dr. Norbert Gattermann (Heinrich-Heine-University, Düsseldorf, Germany) explained that the risk of death due to causes other than leukemia rises dramatically in patients who have MDS and low hemoglobin counts because of red blood cell shortages. So patients with MDS need regular red blood cell transfusions. However, frequent red blood cell transfusions cause iron overload, which has a negative effect on survival.

Iron overload can affect the endothelium. Endothelial dysfunction increases the risk of stroke and heart attacks. Iron overload might also aggravate bone marrow dysfunction in MDS and start a vicious cycle. Specifically, MDS causes anemia, which leads to the need for red blood cell transfusions, which cause iron overload. Experts hypothesize that the iron overload may cause heart problems and might contribute to the development of new genetic mutations in MDS.

Iron Chelation Treatment

Iron chelation treatment can improve endothelial function in patients with coronary artery disease. This beneficial effect might be important for elderly patients with MDS, who often have blood vessel disease as a part of aging.

Iron chelation can overcome the destructive effects of iron overload. For example, it can improve blood cell formation in a small subset of patients with MDS. The secret to success is maintaining the treatment over a very long time.

A recent study showed that low doses of the iron chelator deferasirox increase the growth of immature red blood cells. This finding led to a phase II clinical trial in France on the effects of early introduction of low doses of deferasirox in patients with low-risk MDS who don’t respond to ESA treatment for anemia.

Another recent study that used data from the Canadian MDS registry showed an impressive difference in overall survival between patients treated with iron chelation and those not treated. An imbalance in some patient characteristics may also contribute to these findings, so the investigators are now doing a more sophisticated analysis of these data.
LIST OF ACRONYMS

AML: Acute Myelogenous Leukemia  
CMML: Chronic Myelomonocytic Leukemia  
ESA: Erythropoietin-Stimulating Agent  
GVHD: Graft-Versus-Host Disease  
HMA: Hypomethylating Agent  
IPSS: International Prognostic Scoring System  
IPSS-R: Revised International Prognostic Scoring System  
MDS: Myelodysplastic Syndromes  
NGS: Next-Generation Sequencing  
WHO: World Health Organization

GLOSSARY OF TERMS

Blasts: abnormal, immature blood cells  
Comorbidities: additional diseases beyond MDS  
Complex karyotype: three or more abnormalities in their chromosomes  
Conditioning treatment: used to kill all remaining cancer cells before stem cell transplantation  
Cytogenetic remission: no detectable chromosome abnormalities  
Cytogenetics: study of chromosomes  
Cytokines: proteins  
Cytopenia: low blood cell count  
del(5q): deletion in the long (q) arm of chromosome 5  
DNA methylation: a process that helps control gene activity, resulting in blockage of cell growth.  
Dysplasia: blood cells in bone marrow with an abnormal appearance  
• Multilineage dysplasia: abnormalities in more than one type of blood cell  
• Single lineage dysplasia: abnormalities in only one type of blood cell  
Endothelium: layer of cells lining the heart and blood vessels  
Erythroid response: According to the 2006 criteria developed by the International Working Group for the Prognosis of MDS:  
• In patients who have not received red blood transfusions—hemoglobin increase of 1.5 g/dl  
• In those who have had transfusions—reduction in transfusions by at least four units of packed red blood cells over 8 weeks compared with the 8 weeks before treatment  
Erythropoietin: a hormone that promotes red blood cell formation  
Gene expression: the process that genes use to make their products, such as proteins

Low White Blood Cell Counts

Dr. Fenaux explained that HMAs, especially during the early cycles, can suppress the bone marrow’s ability to form blood cells. The resulting low white blood cell counts can lead to infections, and the lower platelet counts can cause bleeding. Doctors sometimes use antibiotics or antifungal medicines, among other treatments, to prevent the infections.

The best evidence so far comes from an analysis of data from the European LeukemiaNet MDS. The overall survival of 192 chelated patients was significantly better than that of a comparison group of 573 patients, even after the investigators took into account patient age, sex, other health conditions, ability to perform routine tasks, and number of transfused red blood cell units.
**Graft-versus-host disease (GVHD):** Attack by transplanted cells on the recipient’s body in which the transplanted cells cause inflammation of some normal tissues.

- Acute: within 3 months of transplantation
- Chronic: starting more than 3 months after transplantation

**Graft-versus-leukemia effect:** T cells (part of the immune system) in the donated stem cells can attack the remaining cancer cells

**Haploidentical stem cell transplantation:** the donor’s blood markers match half the patient’s markers

**Histone deacetylase (HDAC) inhibitors:** drugs that interfere with DNA’s ability to control gene activity by inhibiting the histone deacetylase enzyme; can kill tumor cells by stopping them from dividing

**Hypomethylating agents (HMAs):** category of drugs—including azacitidine (Vidaza) and decitabine (Dacogen)—that block the methyl groups attached to genes needed for normal blood cell development, preventing the silencing of certain genes involved in controlling cancer and allowing normal functioning of the tumor suppressor genes

**International Prognostic Scoring System (IPSS):** often used by doctors to classify MDS severity

**Iron chelation treatment:** removes extra iron from the blood

**Iron overload:** too much iron in the blood

**Minimal residual disease:** small numbers of cancer cells that stay in the body after treatment

**Revised IPSS (IPSS-R):** takes more information into account than the IPSS and categorizes patients into five risk groups instead of four

**Ring sideroblasts:** abnormal red blood cells with ring-shaped iron deposits

**Secondary AML:** AML that developed after treatment for MDS or another cancer

**Somatic mutation:** change in a gene that happens after conception in a patient’s cells, is not inherited, and is not passed on to the patient’s children

**Subcutaneous:** under the skin

**Thrombocytopenia:** low platelet count

**Treatment failure:** occurs when a patient doesn’t respond to the treatment, responds only temporarily, or has to stop the treatment because of side effects.

**Variant allele frequency:** frequency of the selected mutated genes

**GENERIC AND BRAND NAMES OF DRUGS**

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More than 20 years ago, the MDS Foundation, Inc. was established by an international group of physicians and researchers to provide an ongoing exchange of information relating to MDS. Until the Foundation was created, no formal organization had been devoted solely to MDS. Due to a persistent rise in awareness and diagnosis of MDS, as well as continued growth in the research efforts surrounding MDS, the need for our Foundation has only increased over time. Each year we continue to expand our reach worldwide to meet the many growing needs of the patients and families affected by myelodysplastic syndromes, as well as the healthcare professionals who dedicate their lives to caring for these patients, and researching treatment options and a cure for this disease.

WE UNDERSTAND WHAT IS IMPORTANT…

For the newly diagnosed patient, offering a balance of education and gentle support, coupled with empowering each patient and caregiver with the tools to self-manage their disease and seek the best options for treatment.

For our healthcare professional partners, offering educational programs that include the latest updates in MDS research, direct access to international working groups dedicated to the study of MDS and MPNs, and, when possible, the funds needed for this research.

For our industry partners, the sharing of information related to treatments and clinical studies, while also working to incorporate the much needed patient voice into these clinical studies. Overall, creating an environment where patients, families, and professionals effectively work together towards the common goals of better treatment options, improved quality of life, and eventually a cure for MDS.

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