



THE MDS NEWS

The Newsletter of The Myelodysplastic Syndromes Foundation

From the Guest Editor's Desk

This month we are fortunate to have two fascinating guest editorials on two very different subjects.

Molecular Abnormalities in Myelodysplastic Syndromes



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Introduction

Peripheral blood cytopenias in combination with a hypercellular bone marrow exhibiting dysplastic changes are the hallmark of myelodysplastic syndromes (MDS). Most of the patients present with signs and symptoms of anemia. Another clinical problem which is related to leukocytopenia is an increased susceptibility to infectious complications. Despite the fact that the bone marrow contains a high number of hematopoietic progenitor cells, there is a dramatic lack of functionally intact peripheral blood cells. Therefore, the underlying mechanism for MDS seems not to be a disturbed proliferation rather than an altered differentiation of hematopoietic cells.

For decades, researchers have been interested in detection and characterization of molecular defects in MDS. Since we have known that other malignant hematopoietic diseases (such as chronic myeloid leukemia) may be caused by single molecular defects, the search for a single significant molecular defect in MDS has not been successful yet and is still ongoing. On the other hand, we have learned the lesson that MDS may not be caused by single changes alone. Typically, MDS develops not very fast and sometimes it lasts several years from the first symptoms to the final diagnosis of MDS and any necessary therapeutic interventions. However, one reason for this slow-going process may be the accumulation of several cellular and molecular defects during the course of MDS. Therefore, this review article will describe a number of molecular changes detected in bone marrow cells of patients with MDS. Referring to the accumulation of cellular and molecular defects in MDS, one proposal for the multistep pathogenesis of MDS is shown in Figure 1. After initial damage of the progenitor cell by a toxin or a spontaneous mutation, several additional alterations may affect these cells providing them with a growth advantage. These alterations can influence expression of cell cycle related genes, transcription factors as well as tumor suppressor genes.

One of the major (technical) problems is that most of the experiments which utilize clinical samples from MDS patients for molecular analyses, are performed with low-density, non-adherent bone marrow cells. This may be adequate for high-risk MDS and acute myeloid leukemia (AML) evolved from MDS because of the more uniform blast population. In contrast, in

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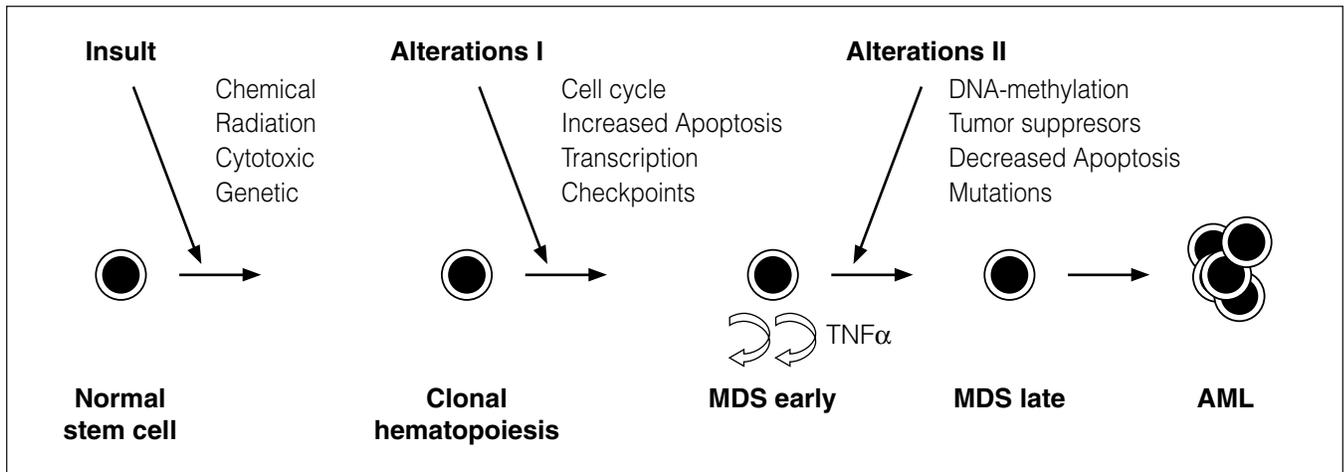


Figure 1. Multistep Pathogenesis in MDS. The initial genetic insult upon the hematopoietic stem cell can be caused by chemicals, radiation, cytotoxic drugs or random endogenous mutations. The accumulation of several alterations which may affect cell cycle control, transcription or tumor suppressors, results in the expansion of the MDS clone. These cells undergo increased apoptosis. The progression to leukemia is probably not dependent on the order of occurrence of genetic alterations but is dependent on the genes that are altered. The final step, leukemic transformation, may be enhanced by alteration of additional genes including tumor suppressor genes and/or by hypermethylation of critical targets. The later stage of leukemogenesis is associated with a decreased apoptosis.

typical low-risk MDS, the bone marrow cells are very heterogenous. Therefore, molecular abnormalities which are characteristic of the malignant cells are much more difficult to find in low-risk MDS as compared to high-risk MDS or AML. Furthermore, the lack of suitable experimental models for MDS, e.g., cell lines or animal systems hampers progress in understanding the biology of this disease. There is a critical discussion as to whether lymphocytes are involved in the clonal hematopoiesis in MDS, but precursors of red blood cells (RBC), platelets, neutrophils, monocytes, eosinophils and basophils are members of the abnormal clone.

Is There a “Philadelphia Chromosome” in MDS?

Bone marrow cells of about 50% of patients show chromosomal alterations at the time of the first diagnosis of MDS. There are common cytogenetic lesions at chromosomes 5, 7, 8, 11, and 20 suggesting that genes located at these sites behave as possible tumor suppressor genes and their alteration is a contributing cause of MDS. On the other hand, there is no known specific molecular alteration which has been shown to be the “major hit” in most of the MDS cases (as it is known from Philadelphia-Chromosome positive chronic myeloid leukemia). Besides specific syndromes (as an example the 5q- syndrome is explained in more detail later in this editorial), there is no molecular alteration which is exclusively associated with a significant

number of patients with MDS. Therefore, there is a need of the application of recent high-throughput molecular techniques to identify key molecular changes in hematopoietic cells from patients with MDS. This may lead to the identification of new targets even for innovative treatment strategies.

5q- Syndrome

This clinically distinct entity involves a deletion of the long arm of chromosome 5 and is characterized by a female preponderance, thrombocytosis, macrocytic, fairly severe anemia often requiring red blood cell (RBC) transfusions, prominent megaloblastoid erythroid hyperplasia in the bone marrow, and megakaryocytes which are large, often greater than 30 μm in diameters, and which often have a single eccentric round nuclei. Interestingly, the rate of leukemic transformation in individuals with 5q- syndrome is only 25% after an observation period of 15 years. The underlying molecular lesion in 5q- syndrome is still unknown. The critical segment may be at chromosome 5q31. The human GRAF gene located in this region can fuse to the MLL gene disrupting both alleles, but the significance of this gene in the 5q- syndrome is unclear. Also, the loss of one allele of one or many genes on 5q (haploinsufficiency) could contribute to the 5q- abnormality. So far, the relationship between the 5q- abnormality and specific subtypes of MDS on a molecular level remains unclear. Application of gene expression profiling as

well as SNP-analysis by microarrays has started to characterize the molecular defects in different types of 5q- abnormalities. It is the hope for the future that this may result in the better understanding of molecular/signal transduction changes in this distinct entity. Interestingly, patients with 5q- syndrome are good responders to treatment with immunomodulatory drugs such as lenalidomide (Revlimid®), but the mechanism of action still remains unclear.

Alteration of Signal Transduction and Cell Cycle Related Genes in MDS

Known abnormalities of signal transduction genes in MDS include point mutations of RAS (frequency of 10-15%). N-RAS is most frequently mutated, with a point mutation occurring at either codon 12, 13 or 61. Mutations of this gene result in an activated protein which stimulates its downstream targets such as RAF and MAPK. Of interest, activation of the RAS pathway is most frequently associated with an abnormality that has a monocytoid-like differentiation including mutated RAS in CMML and mutated NF-1 or PTPN-11 gene in JCMML.

Alterations of the p53 gene occur in about 10% of MDS. Changes are usually missense mutations of one allele with the second allele being lost. Patients, whose abnormal clone has an isochromosome 17q, often have a p53 mutation in their cells. These mutations usually prevent the protein from being able to bind to DNA thus losing its ability to transactivate target genes such as the cyclin-dependent kinase inhibitor (CDKI) p21^{WAF2}. Mutations of p53 are associated with progression of the disease and poor prognosis. Recently, somatic point mutations of several myeloid transcription factors have been demonstrated in patients with AML and MDS including AML-1 and C/EBP α .

One other reason for the abnormal proliferation which is associated with a block of differentiation in MDS may be the disturbance of the mitotic checkpoint CHK2. Elimination of checkpoints may result in cell death, infidelity in the distribution of either chromosomes or other organelles between dividing cells, or increased susceptibility to environmental perturbations such as DNA damaging agents.

A somatic mutation of JAK2 (V617F) was recently described in myeloproliferative disorders, in particular in polycythemia vera rubra. Despite a very low frequency of such JAK2 mutations in MDS, about 8% of patients with CMML (which is now more defined as being part of the myeloproliferative disease group rather than of the MDS group) show the mutation at the JH2 autoinhibitory domain of JAK2. Whether an

increased incidence of this or other JAK2 mutations is associated with the RARS-subtype has to be clarified in further molecular genetic studies. Recently, first reports indicate that the V617F mutation is a rare event in RARS but common in RARS-T, a specific subgroup of RARS associated with a marked thrombocytosis. Patients with this disease present with signs of essential thrombocythemia including a marked increase of platelets in the peripheral blood, a feature not typical for RARS.

Epigenetic Changes

One of the mechanisms to regulate gene transcription is DNA methylation. Many genes have repeated sequences of „CG” nucleotides (CpG islands) within the promoter sequence. Such CpG islands are the target for methylation resulting in either decreased or absent binding of transcription factors to the methylated binding site. As a consequence, the gene will not be transcriptionally activated. DNA methylation is a part of normal regulation of gene expression and may change during hematopoietic differentiation, but aberrant DNA methylation may cause gene silencing of a number of important tumor suppressor genes or cell cycle-controlling genes. Given the principle that malignant transformation of cells may be caused by the biallelic disruption of genes which have a control function (such as the cell cycle or regulation of apoptosis), the first hit may be mutation of one allele whereas the second hit may be gene silencing of the other allele by abnormal DNA methylation. This is an alternative means for the inactivation of tumor suppressor genes in addition to point mutations or gene deletions.

Important genes for cell cycle regulation are the cyclin-dependent kinase inhibitors p15^{INK4b} and p16^{INK4a}. These two genes are rarely mutated or deleted, but transcription of the p15^{INK4b} gene is often silenced due to abnormal methylation of its promoter region. With the availability of demethylating drugs, this specific alteration can be targeted resulting in hematopoietic improvement in patients with MDS.

Summary and Future Aspects

The underlying mechanisms causing primary MDS requires further analysis. Different molecular alterations which have been described, suggest that it is a multistep alteration to the hematopoietic stem cells that include genes involved in cell cycle control, mitotic checkpoints as well as growth factor receptors. Secondary signal proteins and transcription factors which give the cell a growth advantage over

its normal counterpart, may be affected as well. The accumulation of such defects may finally cause the leukemic transformation of MDS.

As outlined at the beginning of this article, one of the central problems is the heterogeneity in MDS. Fortunately, high-throughput molecular techniques such as gene expression profiling and genomics may enable us to achieve a much better understanding of the genetic and molecular basis of MDS. As a hope for the future, microarray analysis may detect gene expression profiles which are strongly associated with different risk-groups in MDS. Furthermore, analysis of global gene expression may provide new insights into alterations of cellular pathways in early hematopoietic stem cells in MDS. This should consequently result in the design/discovery of new target-specific drugs for treatment of MDS.

Finally, it may be difficult in the future to discover the “Philadelphia Chromosome in MDS”, but the combination of different molecular techniques and experimental strategies can ultimately result in a better understanding of the disease.

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Is Myelodysplastic Syndromes “Cancer”?

The Answer May Matter More Than You Think



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Introduction

Some doctors have no qualms about using the term “cancer” when discussing a new diagnosis of myelodysplastic syndrome (MDS) with a patient. But other physicians take great pains to distinguish MDS from cancer, outlining the important nuances distinguishing MDS from acute leukemia and other forms of malignancy. Who is right?

At some level, both physicians are being truthful. How to answer the questions that almost all patients ask at some point—“Is MDS a malignant condition? Do I have a form of cancer?”—is partly a matter of perspective. But it is also true that whether to call MDS “cancer” is more than simply semantics: decisions about terminology not only frame how physicians and patients think about and approach these troublesome bone marrow conditions, but may also have significant practical consequences.

How Current Terminology Developed

The current language used to describe MDS resulted from a series of historical developments with respect to how disorders of blood and bone marrow are described and understood by the biomedical community. Back in the 1920s, when the field of clinical hematology was in its infancy, patients with pernicious anemia—a condition due to vitamin B₁₂ deficiency that results in blood changes and eventually spinal cord deterioration—were treated successfully for the first time, using extracts of animal livers. Subsequently, patients who had been thought to have pernicious anemia but who unexpectedly did not respond to liver extract therapy were labeled as having “refractory anemia” (i.e., anemia that is resistant to treatment). Then, in 1953, a group of academic physicians in Chicago described a small group of patients who suffered

from a previously unrecognized syndrome that was characterized by anemia and peculiar bone marrow abnormalities. This new syndrome initially appeared distinct from acute leukemia, but over the course of a few months or several years it often progressed to become acute myeloid leukemia (AML). Therefore, the condition became known as “pre-leukemia” or “smoldering leukemia”.

By the 1970s, it was clear that “refractory anemia” and “pre-leukemia” were really two sides of the same coin, and the term “myelodysplastic syndromes” (MDS) came into widespread use to describe both conditions. This new name, as well as the widely used MDS classification systems developed during that era (i.e., the 1976 and revised 1982 French-American-British classification systems), reflected the fact that while most patients with MDS are simply anemic, some also have bone marrow failure that is associated with an accumulation of leukemia-like blast cells. Both of these groups of patients have a risk of ultimately progressing to AML, but many patients with early forms of MDS do not ever do so—in this latter group, there are many more deaths from complications of low blood counts (especially infections and bleeding) or causes unrelated to MDS than from AML. “Pre-leukemia” was felt to be an inaccurate and incomplete descriptor for the low-risk MDS group in particular, and its use fell out of favor. The term “refractory anemia”, however, was retained to describe a stage of MDS that carries a relatively good prognosis compared to other stages such as “refractory anemia with excess blasts”.

Disease Classification

Because of this irregular history and past uncertainty about the connection of MDS to AML, classifications of disease such as those periodically published by the World Health Organization (WHO) have not always designated MDS as a form of malignancy. As a result, agencies that are devoted to the study of cancer, such as the National Cancer Institute in the United States, have not tracked MDS cases until very recently. This has led to difficulty in knowing just how many patients are affected with MDS in the US or in other countries with a similar health administrative structure. While there are good state and national registries for cancer incidence, the quality of disease registries for non-malignant diseases varies, and many non-malignant conditions—including most forms of anemia—are not systematically tallied at all. The most recent disease classification published by WHO in 2002 now clearly designates MDS as a form of hematopoietic

neoplasm—that is, a type of malignancy, or a cancer of the bone marrow. This revision changes how the syndrome is viewed from an administrative standpoint, and hopefully the change will lead to more accurate epidemiological studies in the future.

Biological Similarities

The WHO re-classification recognized that there are significant biological similarities between MDS and other malignancies. For instance, cells in the bone marrow of MDS patients grow and proliferate without much consideration for their surrounding environment, and many cells are identical or nearly-identical copies of each other, known as “clones”. The presence of a clone is a hallmark of cancer, as is unregulated cell proliferation, but neither feature alone is enough to define cancer. In fact, the term “cancer” has proven surprisingly difficult to define. As Supreme Court Justice Potter Stewart once famously quipped about obscenity and pornography, “I can’t define it... but I know it when I see it.” The same might be said of cancer—physicians know exactly what they are talking about when using the term or looking at an X-ray full of metastatic tumors, but most of us stumble a bit when asked to give a robust definition.

In addition to cancer-like features of cells, the genetic abnormalities (including broken and lost chromosomes) that are typical of MDS are also quite typical of other forms of malignancy. For instance, there is also a lot of overlap between the specific chromosome abnormalities and DNA point mutations found in MDS and those found in AML, and acute leukemia is a condition which no one would deny is a type of cancer—even though leukemia cells don’t usually form a “lump” or a well-defined nodule, in contrast to the common “solid tumor” cancers that develop in the breast, lung, colon, prostate, and other organs. Likewise, the distinction between the WHO definition of the MDS subtype *refractory anemia with excess blasts* and the WHO definition of AML is arbitrary, an administrative distinction rather than a biological one: a proportion of undifferentiated blasts in the marrow of 20% or greater defines AML, whereas less than 20% blasts represents MDS. Thus, if one were to argue (as some have done) that MDS is not a form of cancer, but AML is, one would be forced to explain why a patient with 19% bone marrow blasts (i.e., MDS) does not have a form of cancer, while a similar patient with 21% bone marrow blasts (i.e., AML) does have cancer. This is a difficult and

hair-splitting separation, since such patients would be expected to have a nearly identical prognosis, treatment options, and overall disease experience.

Other Disorders in the “Shadowlands” Between Being Benign and Malignant

One important caveat here is that not all conditions that are clonal are considered cancer, as mentioned above. For example, a large proportion of otherwise healthy people develop clonal proliferations of plasma cells (“monoclonal gammopathy of undetermined significance” or MGUS), B cells (“B cell clone of undetermined significance” —BCUS—and stage 0 chronic lymphocytic leukemia), or of the lining of the colon (i.e., benign, non-invasive adenomatous colon polyps) as they get older. These conditions are exceedingly common, and often cause no trouble. More than 3% of the population over 70 have a MGUS, and only a few of them (about 1% per year) will go on to develop multiple myeloma, lymphoma, or another form of aggressive cancer. Even in low risk populations, more than 10% of people over the age of 50 have colon polyps, but most of those polyps will never become an invasive malignancy.

The major distinction between these clonal conditions and the disorders more typically labeled “cancer” is largely a product of how these disorders are treated, and the overall prognosis that they convey. MGUS, BCUS, and stage 0 chronic lymphocytic leukemia do not usually require any treatment and are best approached by watchful waiting and periodic retesting (e.g., once a year). And of course, the reason all persons above the age of 50 should have a colon examination is because colon polyps are easily detectable and can be cured by resection, which prevents their eventual progression to colon cancer—progression that is similar to how MDS can segue into AML. Unfortunately, there is no comparable simple method of eradication of early MDS, because of the diffuse way the cells are scattered throughout the bone marrow.

As with MGUS and BCUS, many patients with early forms of MDS require no specific therapy. However, some patients with early MDS already have quite troublesome blood count abnormalities, or may have worrisome high-risk chromosomal abnormalities that suggest a high likelihood of eventual AML progression. A poll of physicians at 102 MDS Centers of Excellence was conducted in 2004–2005 by the MDS Foundation

and presented by Dr. Alan List at the 2005 Annual Meeting of the American Society of Hematology. This study revealed that among patients with earlier forms of MDS (Low- and Intermediate-1 Risk Category disease, as measured by the International Prognostic Scoring System), 41% of patients were being treated with supportive care alone (mostly transfusions and growth factors), 25% were being followed expectantly, and only 34% received active treatment. In contrast, in later, more advanced forms of MDS (IPSS Intermediate-2 and High-risk groups), 63% of patients were receiving active treatment, 30% received supportive care alone (a group that included many too old or too sick to receive more aggressive therapy), and only 7% were being observed without any specific therapy. These numbers describe what is actually being done, not necessarily what should be done, but they do show how MDS, especially higher-risk MDS, is viewed and managed quite differently from most other disorders in the grey-area “shadowlands” between clearly benign and clearly malignant conditions.

Practical Considerations

In North America, most patients with MDS are cared for by physicians who are designated as hematologist-oncologists. This type of physician has undertaken specialized training not only in diagnosis and management of disorders of the blood (hematology), but also in the care of patients with cancer of various types (medical oncology), including the common “solid tumors” mentioned above. Patients with MDS may be treated in a chemotherapy unit attached to the hematologist-oncologist’s clinical facility or an area hospital; such units are primarily filled with people receiving treatment for solid tumors.

Some of the drugs that are commonly used for the treatment of MDS, such as azacitidine (Vidaza®) or decitabine (Dacogen®), were first pioneered as treatments for solid tumors and leukemia. However, in general, in MDS these sorts of agents are used in lower doses and different treatment schedules, and with different biological goals, than when they were first used as anti-cancer therapy beginning in the 1960s. Researchers who are looking for money to study MDS and improve therapy for these troublesome conditions have learned to play to both sides of the aisle with respect to whether MDS is a cancer or not, in order to have the best chance of getting their proposed projects funded. When applying for a grant from an agency such as the

National Cancer Institute (NCI), most researchers emphasize the ways in which MDS is like cancer in their grant applications. In contrast, when applying to grant giving agencies who support primarily research in non-malignant diseases, such as the National Heart, Lung, and Blood Institute (another branch of the National Institutes of Health), researchers will often describe MDS primarily as a bone marrow failure syndrome. This isn't being dishonest—both are certainly true—and the ultimate goal is laudable, obtaining funding to try to do a better job of diagnosing and treating MDS, regardless of the semantics about how it is described.

Cancer Insurance

Fears of what is implied by the term *cancer* (it is certainly a loaded word) have led some people to buy health care policies marketed as “cancer insurance”. The magazine *Consumer Reports* recently discussed such policies in an article bluntly entitled, “Insurance You Don't Need”. As the Consumer Reports staff learned, the problem with these sorts of cancer-specific policies is that they often provide less health care coverage at a greater cost than a general health insurance policy does, and diagnosis and treatment of cancer is always covered by general health insurance policies anyway. I have cared for a few patients diagnosed with AML who had a cancer insurance policy and received a payout that was very helpful to their families, but it has been my personal experience that patients with such cancer insurance policies who develop MDS have no luck in obtaining any money from the insurance companies, regardless of how aggressively they are supported by their doctor. This can be very upsetting to patients who were expecting a windfall from their cancer insurance policy to help them cover their medical bills and get them and their families through a difficult time. The insurance policy underwriters simply do not recognize MDS as a form of cancer, even with the new WHO classification and regardless of all appeals to the contrary, because it is in their best interest not to do so, and patients agree to a list of specific covered diseases when they buy the insurance policy, whether they know it or not.

Conclusion

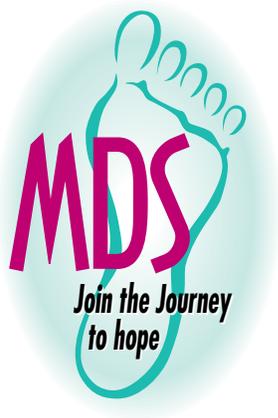
People react differently to hearing the term *cancer*. Even though a lot of research progress has been made in the treatment of malignant diseases, for some people cancer remains an evil word that

conjures up gloomy images of bald-headed, wasted patients wracked by intractable pain and vomiting and “given only months to live”. Some people may have known friends or family members who became very sick from chemotherapy (especially if the chemotherapy was given in the years before modern anti-nausea medications and pain control principles), or who died from an aggressive, refractory form of cancer. Thus, when they or a loved one receives a diagnosis of MDS, thinking of this disorder as a kind of cancer may be very hard, bringing back many difficult memories. If you are one of these people and the word cancer scares you, it is O.K. to think of MDS as a disorder of bone marrow failure, or as a condition of inadequate production of healthy blood cells.

However, many areas of the developing world have a lot of special, helpful resources for patients with cancer. For instance, support groups of people with similar diseases can offer patients tremendous encouragement and strength. So if you have MDS and cancer is just another word to you without an emotional impact, or if you feel that you would benefit from a support network that is available only to cancer patients, then it is also O.K. to think of yourself as having a form of bone marrow cancer—though you should clearly understand your own prognosis and how it might differ from those with more aggressive forms of malignant disease. Any patient with MDS has a risk of developing AML some day, but it is important to keep in mind that inadequate blood counts are really the major issue for most patients.

MDS Essentials E-Newsletter

The Foundation has created a new electronic E-Newsletter to provide healthcare professionals and patients from around the world with timely information, in a cost effective manner. The MDS Essential E-Newsletter is the electronic version of our quarterly newsletter. Receive up-to-date information on clinical trials, research and news by simply subscribing online at www.mds-foundation.org.



From the Operating Director's Desk

Kathy Heptinstall
Operating Director

The MDS Foundation

This year has flown by and it is hard to believe that we are finalizing plans for our 9th consecutive Friday Satellite Breakfast Symposium —Paradigms in MDS Prognosis and Treatment— on December 8, 2006 in Orlando!

As I review what has been accomplished by the Foundation in 2006 and think about our plans for 2007 (and beyond), I cannot help but reflect on the change in the 'landscape' of MDS since the Foundation's inception in 1994.

The world of the MDS patient in 2006 is certainly different from that of the typical MDS patient in 1994. In 1994 there were no active treatments for MDS or even a glimmer of hope for active treatment. Supportive care was the standard and MDS patients had very little hope for the future. In 2006 three approved treatments for MDS (Vidaza®, Revlimid®, and Dacogen®) provide options for the physicians who treat MDS and for their patients. An oral iron chelator (Exjade®) is available in the US and joins desferox in the EU market and provides an option to the inconvenient and uncomfortable Desferal® pump for red blood cell transfusion-dependent MDS patients.

While these treatments provide improved quality-of-life and new hope for MDS patients there is also excitement and hope in the rapid expansion of knowledge about the basic science of MDS, the clinical trials that are being conducted utilizing combination therapy with the approved agents, and the large number of investigative agents for MDS that are in the pipelines of many, many pharmaceutical and biotechnology companies worldwide. Unlike 1994, MDS is now on the front burner of new research and MDS patients have unmistakable hope for the future!

2007 and Beyond

Looking forward to the Foundation's 2007 plans and beyond, we are pleased to note that the 9th International Symposia on MDS (sponsored by the MDS Foundation) will be held May 16–19, 2007 in Florence, Italy. This issue contains key information and updates from Dr. Mario Cazzola and the Scientific Committee for this important biannual event. We hope that you will join us in Florence!!

Information will also be available at the MDS Foundation's booth #2245 regarding the initial plans for the 10th International



The journey began in Paris with the French-American-British group's classification of MDS as separate from acute leukemia. The journey continues today...





Symposia on MDS that will be held in Patras, Greece in the Spring of 2009. Dr. Nicholas Zoumbos will serve as Chairman for that event!

As publicized over the past year our MDS Awareness Program continues to grow. Segment 3 is currently available. If you are interested in participating in this state-of-the-art continuing education program, please join us through the Foundation's website (www.mds-foundation.org) or call 1-800-MDS-0839. All programs have been translated into French, Italian, Spanish, German, and Japanese and are available on our website or by contacting the Foundation.

In 2007 a charity golf tournament to benefit our Young Investigator Grant Program will be held at Innisbrook Golf Resort in Tampa, Florida on February 19, 2007. This is the inaugural MDS Foundation–H. Lee Moffitt Cancer Center Charity Tournament for MDS and will supply the Foundation with additional funding for this important program as well as providing funding for MDS research at Moffitt under Dr. Alan List's direction.

The Foundation has established its first European office at King's College in London. Dr. Ghulam Mufti of King's College has generously donated office space and office equipment to the Foundation. We are in the process of recruiting a Patient Liaison for this office to assist patients in Europe with referrals and other assistance. This office will report directly to the Foundation's main office in Crosswicks, New Jersey. This much needed expansion will greatly benefit patients across Europe.

I would like to thank our supporters on behalf of the Foundation and its Board of Directors. These supporters, first and foremost, are the MDS patients, their families and friends, who form the core of this Foundation. You are our center and the reason that the Foundation exists. We work for you!

The second group that we would like to thank are the pharmaceutical companies that provide us with so much support and assistance. This assistance is given in the form of grants that fund programs that are non-product related but, rather, are geared toward improved disease knowledge and patient support. We could not do the work we do without this type of support.

From all of us at the Foundation, I wish you a wonderful Holiday Season and a safe, happy, and hopeful 2007!!

About the Foundation

The Myelodysplastic Syndromes Foundation was established by an international group of physicians and researchers to provide an ongoing exchange of information relating to MDS.

Until the Foundation was set up, no formal working group had been devoted to MDS. During the past decade we have conducted eight international symposia—in Austria, England, the United States, Spain, Czech Republic, Sweden, France, and Japan. The Ninth International Symposium is being held in May 2007 in Florence, Italy.

A major Foundation effort is our international information network. This network provides patients with referrals to Centers of Excellence, contact names for available clinical trials, sharing of new research and treatment options between physicians, and extension of educational support to both physicians and patients.

In response to the needs expressed by patients, families, and physicians, we have established Patient Advocacy Groups, research funding, and physician education.

The MDS Foundation is a publicly supported organization, exempt from federal income tax under section 501(C)(3) of the IRS code.

Our Website

The MDS Foundation webpage is for healthcare professionals, patients, and other interested people. The Professional Forum and the Patient Forum are integral parts of our website.

The website is constantly being updated to better serve the needs of our patients, their families, and the physicians who treat them.

Please visit us at <http://www.mds-foundation.org>

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Tel: 1-800-MDS-0839
Fax: 609-298-0590
Outside US: 609-298-1035**

Please join us for the 2007 MDS Foundation Golf Tournaments



February 19, 2007

Myelodysplastic Syndromes Foundation – H. Lee Moffitt Cancer Center Charity Golf Tournament for MDS

***Innisbrook Golf Resort –
Copperhead Course, Tampa, Florida***

**Presented by Bruce Fleisher
(PGA Champions Tour Professional)**

Registration and Clinic 8:30 am
Texas Shamble Shotgun 11:00 am

Special events include:

- **Celebrity Pairing Party, Sunday, February 18, 2007**
A chance to mix and mingle with the participating celebrities and PGA Champions Tour Professionals
- **Clinic and Small Group Instruction from the Pros**
- **Awards Dinner and Live Auction**
Including Fabulous Golf Packages with some of the Top Players on the Champions Tour!



August 6, 2007

The Jack Keating Memorial Golf Tournament for MDS

***TPC at Jasna Polana
Princeton, New Jersey***

The MDS Foundation would like to express our gratitude for the generous support given by Celgene, MGI Pharma, Pharmion, Novartis Oncology, Genzyme, and Telik. Our sponsors help support the important work of The MDS Foundation in assisting MDS patients and furthering research for these diseases. The money raised through this tournament will provide Young Investigator Grants for Fellows in Hematology working in MDS. Last year, the Foundation initiated this series of grants, two awards will be made this year and subsequent awards will be granted annually.

We hope everyone enjoyed themselves and will reserve the date of August 6, 2007 for next year's tournament.

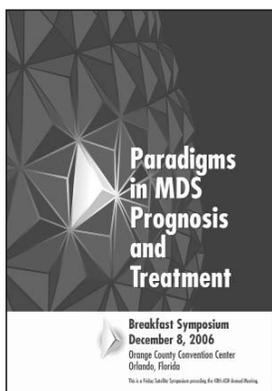
Please contact the MDS Foundation, Inc:
Tel: (800-MDS-0839)
E-mail: kweaver@mds-foundation.org or
nvolpe@mds-foundation.org
Log on to our golf website:
www.mdsgolftournament.golfreg.com

MDS Program to be held at the 2006 Meeting of the American Society of Hematology

BREAKFAST SYMPOSIUM

Paradigms in MDS Prognosis and Treatment

December 8th, 2006



**Orange County
Convention Center,
Orlando, Florida**

**Symposium Breakfast:
Rooms WF 1, 2 & W240**

**Symposium Meeting:
Rooms WF 3, 4, & 5**

- Seating will be on a first-come, first-served basis.
- Breakfast is 7:00 to 7:30 a.m.

- The first 1,000 people will be accommodated.

Visit the MDS Foundation Booth: #2245

This symposium will be available on CD-ROM on December 9th at The MDS Foundation booth.

Agenda

7:30 am–7:45 am

Program Overview and Objectives

Alan F. List, MD, Chairman

7:45 am–8:20 am

Evolution of MDS Morphologic and Response Assessment Criteria

John M. Bennett, MD

8:20 am–8:55 am

Interrogating Less Common Genetic Abnormalities in MDS

PD Dr. Detlef Haase

8:55 am–9:30 am

Therapeutic Targeting of the EpiGenome in MDS

Michael Lübbert, MD, PhD

9:30 am–10:05 am

Integrating Transfusion-Dependence and Iron Chelation into Prognostic and Management Models in MDS

Luca Malcovati, MD

10:05 am–10:40 am

Emerging Treatment Strategies in MDS

Alan F. List, MD

10:40 am–11:00 am

Questions/Answers/Discussion

Alan F. List, MD

Program Overview

Knowledge of the dynamic pathogenesis of MDS as characterized by clinical parameters, laboratory findings, bone marrow morphology, and chromosomal status is essential to accurate initial and ongoing categorization of MDS patients and are predictive not only of the clinical course of the disease but also of probable response to specific treatments. This symposium will focus on evolving morphologic and response assessment criteria, the impact of clonal karyotypic abnormalities and acquisition of new abnormal karyotypes (including lesser known genetic abnormalities) as they relate to disease progression, implications of current molecular genetic research on therapeutic targeting of the epigenome, the effect of transfusion-dependence and chelation therapy on prognosis, and the need for targeting, monitoring, and evaluating therapeutic interventions based on disease stability or progression.

Accreditation

This activity has been reviewed and is acceptable for up to 4 Prescribed credit hours by The American Academy of Family Physicians. AAFP Prescribed credit is accepted by The AMA as equivalent to AMA PRA Category 1 for The Physicians' Recognition Award. When applying for the AMA PRA, Prescribed hours earned must be reported as Prescribed hours, not as Category 1. (This statement applies to all Physicians, not just Family Physicians). Educational Review Systems is an approved provider of continuing education in nursing by ASNA, an accredited provider by the ANCC/Commission on Accreditation.



Foundation Awards Grants



THE MDS FOUNDATION

"HELPING YOU GIVE HOPE..."

THE YOUNG INVESTIGATOR GRANT PROGRAM FOR FELLOWS IN HEMATOLOGY

In December 2005 The Myelodysplastic Syndromes Foundation, Inc., initiated a series of grants "The Young Investigator's Grant Program for Fellows in Hematology". These awards are granted annually.

In 2005, the Grant Review Committee selected Dana E. Rollison's grant submission entitled "Case-control Study of Telomerase Reverse Transcriptase and Telomere Length in Myelodysplastic Syndromes" and Thorsten Braun's submission entitled "NF-kappaB as a Therapeutic Target in Myelodysplastic Syndromes" as inaugural recipients of these prestigious awards.

The 2007 Recipients Are:



Martin Jädersten, MD
Karolinska Institutet, Karolinska University Hospital Huddinge,
Stockholm, Sweden



Arjan A. van de Loosdrecht, MD, PhD
VU University Medical Center, Amsterdam,
The Netherlands

The Foundation is dedicated to furthering the reasearch into MDS and invites Young Investigators (under the age of 40) to submit either basic or clinical research proposals into the causation, epidemiology, molecular biology, cytogenetics, morphology, prognosis, or management of the Myelodysplastic Syndromes.

THE YOUNG INVESTIGATOR GRANT PROGRAM
is supported by the
MDS Foundation-H. Lee Moffitt Cancer Center Golf Tournament for MDS:
February 19, 2007
and the
Jack Keating Memorial Golf Tournament for MDS: August 6, 2007
Presented by Bruce Fleisher, PGA Golf Professional and the MDS Foundation, Inc.

Platinum Sponsors:



Silver Sponsor:



Bronze Sponsors:



The application deadline for 2008 grants is June 15.
Notification of the awards will occur by October 1, 2007 with activation on January 1, 2008.

The MDS Foundation is pleased to announce our second annual series of grants for The Young Investigator's Grant Fund for Fellows in Hematology from institutions that form the Myelodysplastic Syndromes (MDS) Centers of Excellence. Two awards will be made this year and subsequent awards will be granted annually.

This year's recipients will be honored at our second annual luncheon on December 8th at the Rosen Centre Hotel (9840 International Drive, Orlando, Florida) Salon 16 from 11:30 am to 1:00 pm in conjunction with the American Society of Hematology's annual meeting. The Grant Review Committee selected Dr. Arjan A. van de Loosdrecht's grant submission entitled "Multicolour Flow Cytometry in Myelodysplastic Syndromes" and Dr. Martin Jädersten's submission entitled "The Role of the SPARC Tumor Suppressor Gene in the Pathogenesis and Treatment of MDS with 5q Deletion". As this year's recipients, each will be awarded a \$40,000 grant for continued research.

The application deadline for 2007 grants is June 15. Notification of the awards will occur by October 1, 2007 with activation on January 1, 2008. These awards will provide \$40,000 over a 24-month period from January 1, 2008 to December 31, 2009.

Foundation Initiatives for 2007 and Beyond...

The MDS Foundation is committed to making a significant contribution to the advancement in understanding and of accurately diagnosing the myelodysplastic syndromes. We will be focusing our efforts in the following initiatives:

- **ADOPT Registry: ATG Dose, Outcomes, and Patient Identification**



Sponsored by a grant from: 

- **Patient Quality-of-Life Forums**

- **Worldwide Patient Support Groups**

Sponsored by grants from:



- **9th International MDS Symposium, Florence, Italy: May 16–19, 2007**

Sponsored by grants from:



- **CME Awareness Program**

Translations available in Spanish, French, Italian, German and Japanese.

Sponsored by grants from:



- **Differentiating Anemia (CME Program)**
- **MDS Practice and Treatment Survey**
- **The International Working Group on MDS Morphology**
- **Transfusion Burden Registry**
- **The International Working Group on MDS Cytogenetics**

Sponsored by grants from:



MDS Patient Registry

The patient registry form has been revised and a patient authorization form has been developed to meet the new HIPAA guidelines. The Patient Registry will help further research into the etiology, diagnosis and treatment of MDS. Currently, the MDS Patient Registry is only accepting patients through our designated Centers of Excellence. A two page data sheet will be forwarded to investigators who wish to contribute patient's names to the Registry. The Registry is located at the MDS Foundation's Statistical Center at the University of Rochester Cancer Center.

The Foundation looks forward to building the Patient Registry with our Centers of Excellence. If you would like to become a Center of Excellence, please contact The Foundation at the address below.

The MDS Foundation, Inc.

36 Front Street
P.O. Box 353
Crosswicks, NJ 08515

Phone: 1-800-MDS-0839 within the US
Outside the US only: 1-609-298-6746
Fax: 1-609-298-0590

- **CE Awareness Program for Nurses**

- **CE Awareness Program for Pharmacists**

The 9th International Symposium on MDS

May 16–19, 2007
Florence, Italy



ORGANIZING COMMITTEE

Mario Cazzola, *Chairman*
Alberto Bosi, Cristina Mecucci, Valeria Santini

GENERAL INFORMATION

Meeting Location

Palazzo dei Congressi
Piazza Adua 1
50123 Firenze

The meeting venue is very close to the central railway station (Santa Maria Novella).

Hotel Accommodations

The list of hotels will be available on this web site after November 1st, 2006, together with detailed information for hotel reservation.

Registration

Registration fee will be Euro 375,00 within February 28, 2007, and Euro 425,00 thereafter. Registration information will be available on this web site after November 1st, 2006.

Young Investigator Awards

The organizers will establish awards for young investigators who will submit the best abstracts, specifically intended to cover their registration fees and at least part of their travel and accommodation expenses. Ad hoc information will be available on this web site after December 1st, 2006.

Social Program

Ad hoc information will be available on this web site after November 1st, 2006.

PRELIMINARY SCIENTIFIC PROGRAM

Wednesday, May 16th, 2007

- 16:00–18:15 Opening lectures
18:30 Opening ceremony and welcome party

Thursday, May 17th, 2007

- 8:30–10:00 Invited lectures on molecular basis and pathophysiology of MDS
10:00–10:30 Coffee break
10:30–12:00 Invited lectures on clonal proliferation and clonal dominance in myeloid disorders
12:00–13:30 Sponsored symposium
13:30–14:30 Open time for lunch
14:30–16:00 Sponsored symposium
16:00–18:00 Simultaneous oral sessions
18:00–19:30 Poster sessions (wine & cheese)

Friday, May 18th, 2007

- 8:30–10:00 Invited lectures on prognostic factors
10:00–10:30 Coffee break
10:30–12:00 Invited lectures on peculiar nosologic entities
12:00–13:30 Sponsored symposium
13:30–14:30 Open time for lunch
14:30–16:00 Sponsored symposium
16:00–18:00 Simultaneous oral sessions
18:00–19:30 Poster sessions (wine & cheese)

Saturday, May 19th, 2007

- 9:00–10:30 Invited lectures on treatment of myelodysplastic syndromes
10:30–11:00 Coffee break
11:00–12:30 Invited lectures on treatment of myelodysplastic syndromes
12:30 Closing remarks



Membership Information

The MDS Foundation would like to have you as a member. Membership is US\$35 a year for physicians and other professionals. Patients, their families, and others interested in MDS may join at the reduced rate of \$20.

Membership benefits include quarterly issues of the *MDS News*, a special subscription rate of \$109 for *Leukemia Research* (a substantial discount from the current institutional subscription rate of \$2,373), and the worldwide Centers of Excellence patient referral service.

If you would like additional information, please contact us at:

The MDS Foundation
36 Front Street
P.O. Box 353
Crosswicks, NJ 08515
Phone: 1-800-MDS-0839
Fax: 609-298-0590
Outside the US only:
609-298-1035

CALL FOR ABSTRACTS

We invite all investigators in the field to submit abstracts that contain the latest and most exciting developments in myelodysplastic syndromes research.

Only electronic submissions will be permitted and the abstract deadline will be February 28th, 2007. Instructions on how to access the online submission program will be available on this website after December 1st, 2006.

All abstracts will undergo a full peer-review process. Based on the outcome of peer-review, abstracts will be selected for oral presentation, poster presentation or publication only.

The best abstracts submitted by young investigators will be given ad hoc awards.

For further information please contact:

Symposium Secretariat:
Studio ER Congressi-Gruppo Triumph
Via Marconi 36
40122 Bologna, Italy

Tel: +39 051 4210559
Fax: +39 051 4210174

E-mail: ercongressi@gruppotriumph.it

Symposium Website:
URL: <http://www.mds2007.org>

Patient Referrals

Myelodysplastic syndromes can be difficult to diagnose and treat. It is important for both patients and their families to know that optimal treatment is available and that quality-of-life can be enhanced.

If you would like information about treatment options, research, or quality-of-life, we would be glad to help. The Foundation offers a variety of patient services, including preferential referrals to the Foundation's MDS Centers of Excellence. We can also help identify physicians and centers to support you if you are travelling and need assistance.

Please contact us at: 1-800-MDS-0839 (phone) or 609-298-0590 (fax). Outside the US please call: 609-298-1035. You can visit our website at <http://www.mds-foundation.org>.

Purchase MDS Awareness Pins

The MDS Foundation has enameled lapel pins for you to wear with pride and to increase public awareness about MDS. The pins are available with a \$3.99 donation to The MDS Foundation.



To order your pins, call The MDS Foundation at 1-800-MDS-0839.

This item was created especially for The MDS Foundation to contribute to the effort to help people worldwide living with myelodysplastic syndromes. Your donation will help increase awareness of this little known disease, which is the most common of the hematologic malignancies.

Please ask your family and friends to wear these pins in support of our mission!

Seattle MDS Support Group Has First Meeting at Puget Sound Blood Center

The new Seattle area support and education group for MDS, led by Steve Kessler, met for the first time on October 17 at the Puget Sound Blood Center. Both newly diagnosed and “experienced” MDS patients, along with family members, attended and committed to help with future meetings. Tom Butterworth, Communications Manager at the PSBC, generously arranged for them to have the room, speakers and refreshments.

Dr. Chris Counts related what blood resources were like in 1944, when the King County Central Blood Bank began, and blood could be stored for only ten days. In 1975 the program expanded to eight counties and became regional, so people could get blood from other counties. A central transfusion service is located in Seattle, where the cross matching is done. After blood is drawn prior to a transfusion, it is sent to one of four labs in the area, where skilled staff does nothing but compatibility testing. Centralized records assure that any problems patients have with transfusions are recorded. The staff includes, in part, half of the Hematology faculty at the University of Washington Medical School. There are Transfusion Medicine consultants at the Fred Hutchinson Cancer Research Center and the Puget Sound Blood Center. A staff of nine hematologists are on hand to answer questions from doctors in the community, and clinical research is being done in all areas of blood transfusion medicine. The PSBC also has research labs, a clinical services department for outpatient transfusions (used less often since many hospitals now have outpatient transfusion services), and other services. These include a Tissue Center where bones, skin, heart valves and other tissues are banked for transplantation.

Dr. Terry Gernsheimer, of the Puget Sound Blood Center and Seattle Cancer Care Alliance, taught them about transfusion therapy. Transfusion indications include the need to relieve symptoms of anemia and improve oxygen delivery, to replace rapid blood loss and to improve the ability to clot (by providing platelets and coagulation proteins) to prevent bleeding from a planned procedure or to

stop spontaneous bleeding. She explained that many products come from the donation of one unit of blood. After being put in a centrifuge, the results are packed red blood cells (PRBC) and platelet rich plasma (PRP). The PRP becomes both platelets and plasma, and then fresh frozen platelets (FFP) and cryoprecipitate. All of this comes from one pint of donated blood.

Red blood cells (the donation minus the plasma and platelets) have preservative added so that they can be held for 40–42 days. The total volume is about 350 ml, which is about two-thirds of a pint. There are conflicting opinions about whether fresher blood is better, since some think that there are more adverse patient reactions when the blood is fresher. This is only an issue in people who are sensitive to blood transfusions and are more likely to react.

Dr. Gernsheimer explained the symptoms at different hematocrits. At 27 to 33 there is little to no dysfunction. At 23 there is shortness of breath with exercise, at 18 there is some weakness, at 9 there is shortness of breath at rest, and at 3 to 8 there is heart failure. When you actually feel symptoms depends upon the shape you and your lungs are in, your activity, other illnesses, smoking, etc. It also depends on how long it takes you to get there and the general state of your health. Patients are transfused for symptoms, not necessarily the number of their hematocrit.

Platelets are sticky and patch leaking blood vessels, “calling” other platelets, which are activated to clot. This can also show up as purpura on the skin or petechiae, from pressure on blood vessels with not enough platelets to heal little tears. With MDS, some people can have lots of platelets, but they may not work completely. (White cells also can be numerous but not working efficiently.) People can develop antibodies against platelets or HLA, so they are only given when absolutely necessary. Women make more antibodies if they have had many children. Some people are just “antibody formers.” If you make an HLA antibody, you can destroy platelets before they can work for you.

People are constantly developing little breaks in the mucosa, for which they need platelets for their bodies to repair the damage. When people get down to 10,000 platelets, they start having spontaneous bleeding.

Aspirin and ibuprofen inhibit platelet formation. It takes longer to stop bleeding when the platelet count is fewer than 100,000, so someone at that level might have a transfusion of platelets if

undergoing surgery. It depends on how well the platelets are working. Research is being done now on AMG531, an experimental injection to boost platelet production. Platelets, which are yellow, are given to patients from pooled whole blood (needing the platelets from two to eight units for one unit of platelets) or from removing some platelets from a donor's blood and putting the rest of the blood back into the donor. This can be from a random donor, a family donor or an HLA selected donor. A family donor can be used only after a transplant. Using them before could sensitize the patient before a family member donated marrow. It is important to match for HLA for a bone marrow transplant.

Blood components are often modified before being transfused. Blood can be filtered (resulting in so called "leukopoor" blood), CMV screened and irradiated (especially in someone who is going to get a lot of transfusions, or is very immunosuppressed), all of which will reduce the volume but also reduce potential adverse reactions. Risk of HIV has returned to very low levels, since screening has prevented anyone with a risky history (including tattoos) from donating blood. HIV, Hepatitis C, Hepatitis B and HTLV I and II are very, very rare. Other very rare diseases are also rarely found in donated blood.

Bad reactions to transfusions include fever (1 in 20–100), hives (1 in 50–100), transfusion related lung injury (1 in 500–10,000), severe allergic reaction (1 in 20,000), hemolytic transfusion reaction (1 in 30,000), chest or back pain, shortness of breath, nausea, sense of discomfort, chills, flushing, itching or rash. If you have any of these reactions, even mild, tell the transfusion nurse so that the blood bank will know that you're sensitive. The nurse will turn off the blood and figure it out, then restart it slowly. Reactions usually happen in the first fifteen minutes. Pay attention after the transfusion, and return if there is a problem. If a patient has heart failure, the blood is given slowly and a diuretic is also given. Patients are admitted to the hospital for transfusions if there is a large volume of blood, if blood must be given slowly to avoid volume overload, or if the person has antibodies and has reacted previously. Patients who need blood usually receive a minimum of two units, but it depends on the size of the patient. After many transfusions, patients may experience iron overload, and require medication to excrete it.

Please note that the preceding information is helpful to anyone who is interested in learning more about transfusion therapy.

Please respond to steve@Qamonline.com for attendance at future meetings and/or to have your name added to the mailing list. For additional information, please contact The MDS Foundation at 800-MDS-0839.

Spreading the Word Worldwide

Patient Quality-of-Life Forums

Patient forums have been held to date in:

United States

- New York City, New York
- Tampa, Florida
- Palo Alto, California
- Chicago, Illinois
- Scottsdale, Arizona
- Philadelphia, Pennsylvania
- Pittsburgh, Pennsylvania

Europe

- Paris, France
- Bournemouth, England UK
- London, England UK
- Leeds, England UK
- Edinburgh, Scotland UK
- Marseille, France
- Prague, Czech Republic
- Stockholm, Sweden

Future forums are scheduled in:

- New York City, New York: December 15, 2006
- Chicago, Illinois: January 16, 2007
- Dallas, Texas: January 22, 2007
- Athens, Greece: February 3, 2007
- Florence, Italy: May, 2007
- Seattle, Washington: TBD
- Los Angeles, California: TBD

Share Your Stories

The Foundation would like to invite patients and their families to share their stories with others in the MDS community. Living with MDS poses challenges and many of you have stories that provide hope to others. Please contact the Foundation, if you would like us to publish your story.

My Story...

Ralph Colognori **MDS patient**

56 years old

Westwood, New Jersey

Married for 30 years; father of two

Diagnosed with MDS in January 2006

Blood cell counts currently normal with treatment

It all began last December when I started feeling a little fatigued. I was stacking firewood by the side of my house, and I had to stop frequently to catch my breath. I knew something wasn't right.

Working as a school administrator in a public school district in New Jersey, I usually park my car at work on the third floor and walk up the two flights of stairs for exercise. I noticed that my legs began to feel tired and sore after these usual walks.

Around that time, I was scheduled for an annual physical—I usually get one around the holidays. The doctor performed all the usual blood tests. The next day, I got a call from my doctor stating that my blood test results were “concerning.” I was introduced to a hematologist, who informed me that my hemoglobin, platelets and white blood cell counts were low. The doctor indicated I had one of two conditions—aplastic anemia or myelodysplastic syndromes (MDS). On January 5, I received two units of blood through a blood transfusion and later, doctors performed a bone marrow aspiration. Four days later results of the aspiration confirmed that I had MDS, and my doctors and I started thinking about a plan.

I received two more blood transfusions, which were intended only as temporary solutions. The doctors presented me two options—to join a clinical trial with an unproven therapy or to begin treatment with an FDA-approved therapy. On January 27, I received my first cycle of the approved treatment, Vidaza® (azacitidine).

I really wasn't sure what to expect when I first began treatment. I was simply following professional advice but hoping to avoid the blood transfusions—lengthy and uncomfortable procedures that once resulted in a severe reaction. By the time I went to the hospital, waited to be seen, waited for the blood to arrive, completed the necessary testing and received the transfusion, I lost half a day of work. With Vidaza, I no longer have to spend half a day at the hospital. I make a quick trip to my doctor's office for the injection, and then go home.

I haven't had any reactions to the therapy at all. I was given a pill to prevent nausea, but I didn't have any. The only side effect I have is that I might peel a layer of skin, similar to sunburn, in the area where the shot is given.

In the meantime I attended a class to learn more about bone marrow transplantation. My sister volunteered to donate her bone marrow to me, but unfortunately, we discovered she was not a match. In June, another bone marrow donor was found. Again, to my disappointment, the donor did not pass the physical and was no longer qualified.

My doctors told me that my treatments would take a while to kick in. By the time I had several blood transfusions and three cycles of Vidaza, my blood counts went up, and there was no need for another transfusion. As a matter of fact, the last time I had a transfusion was March 9, 2006.

On June 19 another bone marrow aspiration was performed and my doctors did not find any blasts in the sample. I was no worse than when I started treatment.

Every time I start on a new cycle of Vidaza, my doctors perform blood work first to determine that everything is within the normal range. I just visited my doctor, and my blood work is still normal.

Before treatment or blood transfusions, not only was I greatly fatigued, but I was also much more susceptible to infection and blood loss. In the waiting room of the hospital, I would wear a mask to avoid infection and wash my hands or use antibacterial gels frequently. During the winter I was extra cautious to make sure I didn't catch a cold or flu.

Since my treatment began, I have never missed a day of work and no longer need to take extra precautions with my health. Vidaza has given me more time and energy for my work and my family. I am able to live the life I had before MDS and continue with my normal daily routine. In fact, my

doctor said I can now do all the things I usually do, even gardening.

The uncertainty of my health through this process was frustrating and emotionally draining on my family. My daughter was especially stressed, because she was also managing graduate school coursework. Now that stress is gone.

I am looking forward to seeing my daughter pass her Master's exam, and my son graduate from high school. Also, I am very excited to be celebrating my upcoming 30th wedding anniversary with my wife.

Reprinted from *The Advocate*, Stamford, CT
September 16, 2006

The Perfect Present: Brother Gives Stamford Man the Gift of Life

Vesna Jaksic
Staff Writer, *The Advocate*

STAMFORD—Doug Nelson turned 64 on Sept. 1, but there is another day that he also calls his birthday. It's on June 8 and, according to that birthday, he is not even a year old. That was the day Nelson got a stem-cell transplant to save him from a life-threatening disease.

"My other birthday, that's what I call it," he said. "That's the first day of the rest of my life."

After a routine physical a year ago, Nelson was diagnosed with myelodysplastic syndromes, or MDS, a collection of disorders in which the bone marrow does not produce enough blood cells. With no cure for the disease and his white blood cell count getting dangerously low, Nelson received several rounds of chemotherapy and eventually a stem-cell transplant.

The donor? His identical twin brother.

Doug Nelson and Dennis Nelson said they never attempted to confirm they were identical twins, but suspected so their whole lives.

Their looks and voices are strikingly similar and they have the same mannerisms. They speak of their "twin bond," such as the time they checked into the same hotel a day apart, not realizing they were both visiting the same state at the same time.

So when about 20 friends and relatives checked to determine whether their blood matched Doug Nelson's, his twin brother said he was glad to receive confirmation that they were indeed identical. Their blood matched 100 percent, which many MDS patients are never lucky enough to find.

"We were all hopeful that one of us would be the one and I was kind of glad that I was the one," said Dennis Nelson, 64, who works in real estate in Hilton Head, S.C. "As a twin and as a brother, it's a gift from God that I could save his life. I had that gift, the gift was given to me. And not very often does someone have the gift to save someone's life."

Doug Nelson, who until his medical leave worked as the general manager of Stamford operations for William Raveis Real Estate, said he never experienced any symptoms of his disorder, which was diagnosed after blood tests and a bone marrow biopsy.

"I was feeling fine, working 10- to 12-hour days, I was the type of person who had 200 percent energy every day, could get by on about five hours of sleep," he said. "Here I am living life like nothing can happen and all of a sudden you run into a brick wall and they say you have a life-threatening disease."

MDS may develop after exposure to certain chemicals or radiation, according to the Myelodysplastic Syndromes Foundation. Doug Nelson said he believes he acquired the disease while serving in the Marines in Vietnam.

There may be more than 20,000 new cases diagnosed each year, most in people over 60, according to the Foundation.

Doug Nelson had chemotherapy at Stamford Hospital's Bennett Cancer Center and later at New York's Memorial Sloan-Kettering Cancer Center. As he was preparing for his transplant in New York City, his colleagues in Stamford formed a team of about 115 for the annual Bennett Cancer Center Walk, the largest team in the event.

They raised \$15,000 and put on "Doing it for Doug" T-shirts to show support for the boss who always opened his home for company parties and welcomed phone calls any time of the day or night.

"Warm, welcoming, helpful, how else would you describe Doug?" said Joyce Cebo, a senior sales associate who organized the team in his honor. "He would really do anything for anyone."

Doug Nelson said his sense of humor helped him get through his treatment. He said he looked like the Michelin man when his joints swelled from the liquids he was receiving. He compared his twin to a “lifeline” from the TV show “Who Wants to be a Millionaire?”



Doug Nelson is recovering from a stem-cell transplant he received to combat MDS. The donor was his identical twin brother, Dennis Nelson.

Gil Wheless, Doug Nelson’s partner for 30 years, said he was proud of him for maintaining a positive attitude despite his fear about the transplant.

“One night he awoke and he was absolutely scared to death,” said Wheless, 64, a landscape architect. “He basically said, ‘Hold me, I am scared to death.’ That was probably when it was coming down to the point that we knew that if he doesn’t have this he was going to die.”

During the transplant, Doug Nelson was awake for about 1 1/2 hours as he intravenously received 11 million stem cells that had been harvested from his twin’s blood. His twin, his sister-in-law, his partner and his brother and sister were in the room with him.

“I thought, ‘It’s the first day of the rest of my life and I hope it takes and that I have a future,’” Doug Nelson said. “I wasn’t ready to go. Too much to do.”

Days later, he developed a fever of 105 degrees and his blood pressure dropped to 25. His kidneys were shutting down and he ended up in induced sleep in the Intensive Care Unit for nearly two weeks. Nurses at one point asked the family to return because his time was running out. Wheless asked a friend to call a cemetery.

But one day, Doug Nelson woke up. After 38 days in the hospital, he returned to his North Stamford home on July 7.

The first year after a transplant is crucial because the body essentially has no immunity. So in addition to his one-mile walks in the morning and afternoon rides on his exercise bike to strengthen his muscles, Doug Nelson has to avoid crowds.

He also has to avoid touching objects such as money to help prevent infection. He cannot eat raw fruits and has to make sure his vegetables and meats are well cooked.

When he goes to the grocery store, he wears a mask and gloves. His partner helps ensure their home is always clean and free of chemicals and that towels get washed after each use.

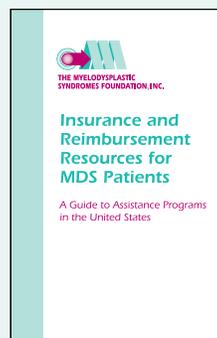
The first 100 days after the transplant are the toughest and Doug Nelson hit that number today. As for his illness, he said the hardest part has been the deaths of both his parents in the spring and not being able to travel to Arizona for the services. He said he is grateful for his family, friends, colleagues and medical staff and believes there is a reason things worked out the way they did.

For example, he said there is a reason that when he finally awoke in the intensive care unit, his twin was the first person he saw. And that there is a reason he made it out alive.

“I feel like I got to the gates and my mother and father just got there and said ‘Get out of here, we’ll see you in 30 years,’ “ he said.

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Now Available From The Foundation



We have assembled a listing of insurance and drug reimbursement resources for MDS patients. It is important to know that there is support for those who cannot afford medicine or other healthcare costs. We hope this new resource will be beneficial in helping you with your medical needs.

This guide to assistance programs in the United States is available for download from the Foundation’s website or can be ordered in booklet form upon request.

ANNOUNCING

MDS Patient Forum to be Held in NYC

FRIDAY, DECEMBER 15th, 2006

Our guest speaker will be Dr. Lewis Silverman from Mount Sinai Medical Center.

This FREE event will be held in New York City from 9:30–2:00 pm. Breakfast and lunch will be served.

This meeting is open to MDS patients and their guests. Patients and their families will have the opportunity to participate in this informal discussion regarding their quality-of-life issues living with MDS. New therapies and patient treatment options will be discussed. You will also be given the opportunity to participate in a question and answer segment.

Upcoming forums will be held in Chicago, Illinois on January 16th, 2007 and Dallas, Texas on January 22nd, 2007.

For reservations and further details, please call Audrey Hassan at 800-637-0839.

Slone Patient Registry

The Slone Epidemiology Center at Boston University is enrolling patients who have recently been diagnosed with myelodysplastic syndromes in a voluntary research project called the Patient Registries at Slone: MDS. The registry gathers important information about the impact of MDS and its treatments on patients' physical, emotional, social, and economic well-being. Participation in the Registry does not affect the care or treatments that patients receive.

You are eligible to join if:

- You have been diagnosed with MDS within the past 3 months
- You live in the US

You do not need to have received any medicines or other treatments for your MDS to be eligible.

For more information or to enroll, visit <http://www.bu.edu/prs/mds>, email mdsinfo@slone.bu.edu, or call the registry at 800-231-3769.

Be a Bone Marrow Donor

For those patients diagnosed with a fatal blood disorder, bone marrow transplantation (BMT) is often the only chance of survival. Related donors provide suitable matches only 33 percent of the time. This leaves nearly 70 percent of patients without a match. The need is especially critical in racial and ethnic minority groups.

Registering as a donor is simple. A blood sample is all you need to enter your tissue type into the National Marrow Donor Program (NMDP) computerized registry. If you are in good health and between the ages of 18 and 55, you can contact NMDP at 1-800-MARROW-2. They will send additional information, including the NMDP center nearest you.

Give the Gift of Life!

OTHER SITES OF INTEREST:

ASBMT™ American Society for Blood and Marrow Transplantation:

www.asbmt.org

International Bone Marrow Transplant Registry:

www.isbmtr.org

National Marrow Donor Program®:

www.marrow.org

Blood & Marrow Transplant Information Network:

www.bmtinfonet.org

Blood & Marrow Transplant Resources:

www.BMTresources.org

Over 140 Things You Need to Know about Your Autologous Bone Marrow or Stem Cell Transplant is available online at www.BMTresources.org

or call (414) 870-4850, ISBN# 0-9768060-0-2/ Price: \$11.95.



Contains over 140 invaluable tips to help transplant patients sail through their procedures.

The Foundation Resource Center is Now Online!

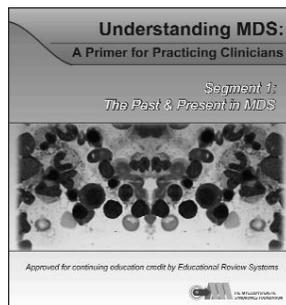
This educational center is designed to provide clinicians, researchers, and other healthcare professionals with a comprehensive source for the latest information and educational programming on the myelodysplastic syndromes.

In the Conference section of our website you can view materials presented at MDS conferences or register for upcoming MDS-related symposia.

Understanding MDS: A Primer for Practicing Clinicians

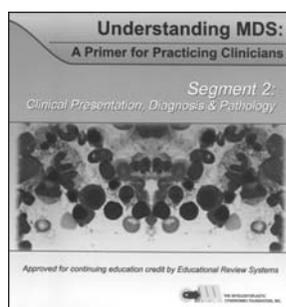
Visit www.mds-foundation.org and click on The MDS Foundation Resource Center to take advantage of this comprehensive program, and other informative programs coming soon, designed to provide you with tools and information that will assist you in administering the best care to your patients.

Segment 1: The Past and Present in MDS.



Segment 1 provides insight into the history of MDS, development of the MDS classification and prognostic systems, and a glimpse into the future of MDS diagnosis, research and treatment.

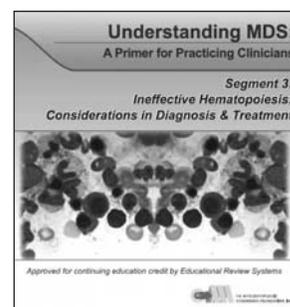
Segment 2: Clinical Presentation, Diagnosis & Pathology.



Segment 2 provides insight into the clinical picture of adult and pediatric MDS, primary and secondary MDS, FAB and WHO Classification system, and rationale for the proposed MDS pediatric classification system.

Segment 3: Ineffective Hematopoiesis: Considerations in Diagnosis and Treatment.

Segment 3 provides insight into the pathogenic mechanisms that contribute to the development of MDS, including the altered bone marrow microenvironment of MDS in terms of cells, cytokines, growth factors, receptors, and microvasculature; dyserythropoiesis in MDS, and therapeutic targets and approved drugs for the treatment of MDS.



This multi-segment program will allow participants to choose the segments that interest them and to learn at their own pace. Segments may be completed via a written program, on-line in our technologically advanced MDS Foundation Educational Center, or via CD-ROM on their personal computer.

The program is approved for 1 hour of CME credit upon completion. There is no charge for this educational activity.

The Myelodysplastic Syndromes Foundation strives to serve as an effective conduit for information regarding the most updated treatment options, clinical studies, referrals to Centers of Excellence, and other information concerning MDS. Please bookmark our site, www.mds-foundation.org, and check back frequently for new, informative programs.

Blood & Marrow Transplant Newsletter

Blood & Marrow Transplant Newsletter is published four times annually by BMT InfoNet.

To subscribe, contact:

BMT InfoNet

2900 Skokie Valley Road, Suite B
Highland Park, IL 60035

Toll free: 888-597-7674

Tel: 847-433-3313

Fax: 847-433-4599

E-Mail: help@bmtinfonet.org

Web: www.bmtinfonet.org

New MDS Publications

Listed below are citations of some new publications relevant to MDS (pathogenesis, clinical characterization, management, etc.). To access the complete article log on to www.pubmed.gov.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, Pinto A, Beran M, de Witte TM, Stone RM, Mittelman M, Sanz GF, Gore S, Schiffer CA, Kantarjian H. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108:419–425.

Kantarjian H, Oki Y, Garcia-Manero G, Huang X, O'Brien S, Cortes J, Faderl S, Bueso-Ramos C, Ravandi F, Estrov Z, Ferrajoli A, Wierda W, Shan J, Davis J, Giles F, Saba HI, Issa JP. Results of a randomized study of three schedules of low-dose decitabine in higher risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood*. 2006 Aug 1 [Epub ahead of print].

Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, Klimek V, Slack J, de Castro C, Ravandi F, Helmer R 3rd, Shen L, Nimer SD, Leavitt R, Raza A, Saba H. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*. 2006;15;106(8):1794-803.

Kuendgen A, Matsuda A, Germing U. Differences in epidemiology of MDS between Western and Eastern countries: Ethnic differences or environmental influence? *Leuk Res*. 2006 Apr 18 [Epub ahead of print].

List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, Powell B, Greenberg P, Thomas D, Stone R, Reeder C, Wride K, Patin J, Schmidt M, Zeldis J, Knight R. Hematologic and cytogenetic response to lenalidomide in myelodysplastic syndrome with chromosome 5q deletion. *New Engl J Med*. 2006; 355:1456–1465.

Mannone L, Gardin C, Quarre MC, Bernard JF, Vassilief D, Ades L, Park S, Vaultier S, Hamza F, Beyne-rauzy MO, Cheze S, Giraudier S, Agape P, Legros L, Voillat L, Dreyfus F, Fenaux P; Groupe Francais des Myelodysplasies. High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. *Br J Haematol*. 2006;133(5):513–9.

McCarthy, Alice. Treatment boost for MDS. *Cure*. 2006;5:6:44.

Milligan DW, Kochethu G, Dearden C, Matutes E, MacConkey C, Catovsky D. Haematological Studies Group, UK National Cancer Research Institute. High incidence of myelodysplasia and secondary leukaemia in the UK Medical Research Council Pilot of autografting in chronic lymphocytic leukaemia. *Br J Haematol*. 2006;133(2):173–5.

We would like to thank Peter Greenberg, member of the MDS Foundation's Board of Directors, for his assistance in monitoring these important publications.

ICD9 Coding Changes

Changes have been made to the ICD9 codes for MDS. The following sequence reflects the WHO plus the now extinct but still classifiable RAEB-T:

Diagnostic Term	ICD-0-3	
Refractory Anemia	C42.1	M-9980/3
Refractory Anemia with Ringed Sideroblasts	C42.1	M-9982/3
Refractory Anemia with Excess Blasts	C42.1	M-9983/3
Refractory Anemia with Excess Blasts in Transformation	C42.1	M-9984/3
Refractory Cytopenia with Multilineage Dysplasia	C42.1	M-9985/3
Myelodysplastic Syndromes (MDS) with 5q-Syndrome	C42.1	M-9986/3
Therapy-related Myelodysplastic Syndromes (MDS)	C42.1	M-9987/3
Myelodysplastic Syndromes, NOS	C42.1	M-9989/3

International Clinical Trials: An Update

NATIONAL CANCER INSTITUTE TRIALS

As we go to press the National Cancer Institute (NCI) has listed more than 100 clinical trials that focus on Myelodysplastic syndromes. Full study information on these trials is available at www.nci.nih.gov. This information includes basic study information, study lead organizations, study sites, and contact information. To access the information:

- Log on to www.nci.nih.gov
- Click on “Finding Clinical Trials”
- On the next screen look for “Ways to Find Clinical Trials” and
- Click on “Search for Clinical Trials”
- Click on “Type of Cancer” and type in ‘myelodysplastic syndromes’
- Hit search

This search will provide you with all the trials currently underway in MDS. You may also sort by trials that only focus on treatment or trials that only focus on supportive care.

To view listings of additional studies you can log onto www.clinicaltrials.gov. You can also contact 1-800-4-CANCER for more information.

If you are an MDS patient, you may wish to discuss a trial with your primary treating physician to see if you qualify as a candidate.

Clinical trials study new interventions (drugs or procedures) to evaluate their safety and effectiveness in humans. Trials follow a careful set of steps, allowing for the systematic gathering of information to answer questions and confirm hypotheses that were formed earlier, in either laboratory experiments or preliminary trials.

A clinical trial falls into one of four phases:

Phase I. This is the first time a drug is used in humans. The trial is designed to determine dosage, route of administration (oral, intravenous, or by injection), and schedule of administration (how many times a day or week). In this phase researchers also begin to determine the drug’s safety. The phase I trial

is normally conducted in healthy adults and enrolls only a small number of people.

Phase II. Patients with the disease receive the drug at dose levels determined in the earlier phase. The phase II trial begins to determine the effectiveness of the drug and provides more information about its safety.

Phase III. The drug is tested alone or against an approved standard drug. The typical phase III trial enrolls a large number of patients. If it is a comparison trial, patients may be randomly assigned to receive either the new drug or the standard intervention.

Phase IV. In phase IV the drug, already approved by the FDA and available to the public, undergoes continued evaluation. The phase IV designation is rare. Some trials—screening studies evaluating supportive care or prevention—are not conducted in phases. In these trials a group following a certain disease combating strategy, such as a detection method, is compared to a control group.

New Research Protocol Listings

The MDS Foundation wants you to know about clinical trials of investigational treatment options for patients with MDS and has updated its International Clinical Trials list on our website and for distribution.

For a detailed listing featuring new protocols, visit <http://www.mds-foundation.org>, email patientliaison@mds-foundation.org, or call 800-MDS-0839 and the current clinical trials will be sent to you under separate cover.

Clinical trials often have very specific eligibility requirements. Please talk with your doctor to help decide which, if any, trials might be right for you.

Please note that the information is provided strictly as a resource and is not an endorsement of any physician, institution or treatment.

Announcing a New Clinical Research Trial for Platelet Transfusion-Dependent Patients With MDS or CMML

Learn More About P02978

The MDS Foundation wants you to know about clinical trials of investigational treatment options for patients with MDS. In the current clinical research trials, all patients will receive therapy with Lonafarnib, an investigational drug that is being evaluated for treating patients with MDS or CMML who have been regularly receiving at least 1 and not more than 8 platelet transfusions every 4 weeks. The medicine is taken by mouth at home, and although patients will be monitored closely, routine hospital stays are not required.

The Myelodysplastic Syndromes Foundation is assisting in the accrual of patients for Clinical Trial P02978 — A Pivotal Randomized Study of Lonafarnib Versus Placebo in the Treatment of Subjects With Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) Who Are Platelet Transfusion Dependent With or Without Anemia.

What is Lonafarnib?

Lonafarnib is a drug that is being investigated to treat patients with MDS or CMML. Lonafarnib is a potent, orally bioavailable, specific inhibitor of farnesyl transferase. Farnesyl transferase is an enzyme that allows a protein, RAS, to adhere to cell membranes and to cause these cells to become neoplastic or cancerous. Lonafarnib blocks farnesylation of RAS and other proteins involved in cell growth and proliferation.

What is the purpose of this trial?

This trial has several goals:

- To measure how effective Lonafarnib is in the treatment of platelet transfusion-dependent MDS patients with or without anemia.
 - This will be determined by whether or not patients need platelet transfusions following treatment with Lonafarnib with no increase in the need for RBC transfusions or decrease in hemoglobin levels.
- To monitor the safety of Lonafarnib among these patients.
- To evaluate hematological response rates.

- To observe the effect of Lonafarnib on red blood cell transfusion requirements.

What are potential side effects?

The most common side effects of Lonafarnib that were seen in previous clinical trials included diarrhea, nausea, vomiting, anorexia, and fatigue. Most of these side effects were mild to moderate in severity.

Who is eligible?

- Patients who have been diagnosed with de novo MDS and who are platelet-transfusion dependent (received at least 1 and no more than 8 platelet transfusions every 4 weeks) with or without anemia
 - This includes refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), and refractory anemia with excessive blasts (RAEB)], refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). Diagnosis must be confirmed by bone marrow aspirate
- ECOG Performance Status 0 to 2
- Patients with anemia (red blood cell transfusion dependent or independent)
- Patients with no prior therapy with farnesyl transferase inhibitors
- Patients with no treatment for MDS with the exception of supportive care
- Sexually active women of childbearing age will need to use adequate birth control methods while in the study and will be required to maintain this method throughout the study

How is the trial designed?

Patients will undergo a 4 week prospective screening period. Lonafarnib is a pill that is taken by mouth every day for 28 days. Patients will begin treatment and will repeat this regimen for at least three cycles (1 cycle = 28 days).

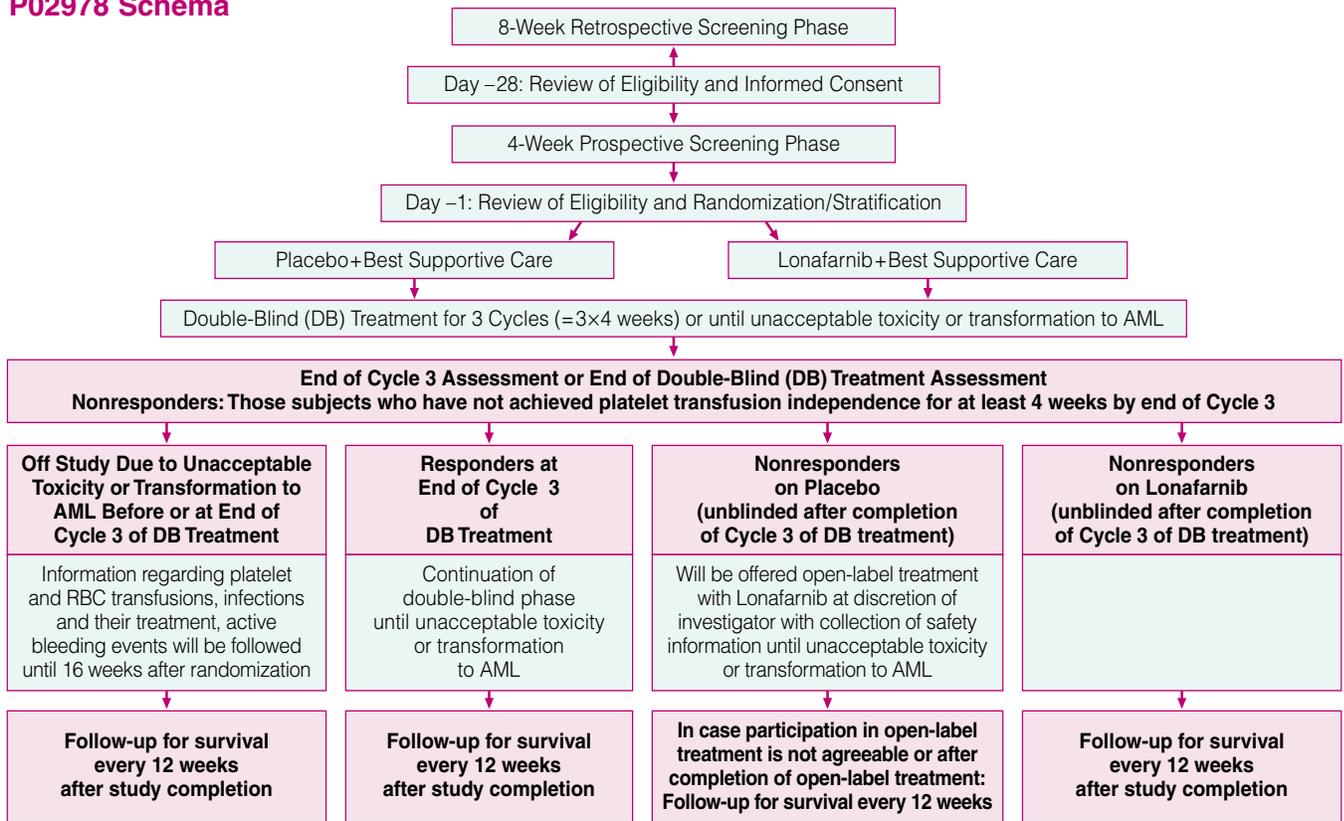
This Phase III trial will be conducted at approximately 60 sites in US, Canada, Europe, Latin America, and the Far East.

In an effort to move the clinical development of Lonafarnib forward as rapidly as possible in the hope of helping platelet transfusion-dependent patients, the Foundation would appreciate hearing from you.

If you are a physician and would like to refer a patient for enrollment into this clinical trial or if you are an MDS patient who receives platelet transfusions, please contact The MDS Foundation at 1-888-813-1260 (outside the US: 609-298-7741).

(continued on page 26)

P02978 Schema



Lonafarnib Clinical Trial Site List (at date of publication)

UNITED STATES

Alvin and Luis Lapidus Cancer Institute
Baltimore, MD
Stephen Noga, MD

University of Minnesota
Minneapolis, MN
Mark Reding, MD

Georgia Cancer Specialists
Tucker, GA
Mansoor Saleh, MD

New York Presbyterian Hospital
New York, NY
Eric Feldman, MD

New York Medical College
Valhalla, NY
Karen Seiter, MD

Bethesda Research Center
Boynton Beach, FL
Roger Brito, MD

University of Massachusetts Medical Center
Worcester, MA
Azra Raza, MD

University of Texas Southwestern Medical Center
Dallas, TX
Robert Collins, MD

James A. Haley Veterans Hospital
Tampa, FL
Hussain Saba, MD

University of South California, Norris Cancer Center
Los Angeles, CA
Dan Douer, MD

Mayo Clinic Hospital
Phoenix, AZ
James Slack, MD

Scripps Cancer Center
La Jolla, CA
James Mason, MD

CANADA / LATIN AMERICA

Canada

Cross Cancer Institute
Edmonton, Alberta
Robert Turner, MD

Sunnybrook Regional Cancer Center
Toronto, Ontario
Rena Buckstein, MD

Princess Margaret Hospital
Toronto, Ontario
Andre Claudius Schuh, MD

Colombia

Fundacion Santa Fe de Bogota
Bogota, Colombia
Monica Duarte Romero, MD

Instituto de Cancerologica SA
Medellin, Colombia
Amado Karduss, MD

Hospital Militar Central
Bogota, Colombia
Benjamin Ospino, MD

Cardio Diagnostico SA

Barranquilla, Colombia
Miguel Urina, ME

Ecuador**Hospital Carlos Andrade Marin**

Quito, Ecuador
Jose Paez, MD

Hospital SOLCA Guayaquil

Guayaquil, Ecuador
Bella Maldonado, MD

Cruz Rojo Ecuatoriana

Quito, Ecuador
Juan Sghirla, MD

El Salvador**Hospital Nacional Rosales**

San Salvador, El Salvador
Hector Valencia, MD

Peru**Hospital Nacional Edgardo Rebaglianti**

Jesus Maria, Peru
Juan Navarro, MD

Puerto Rico**Doctors Cancer Center**

Manati, Puerto Rico
Kenel Fernandez-Barbosa, MD

San Juan Hospital

San Juan, Puerto Rico
Luis Baez-Diaz, MD

San Juan VA Medical Center

San Juan, Puerto Rico
William Caceres, MD

EUROPE / FAR EAST**Austria****University Clinic of Vienna**

Vienna, Austria
Peter Valent, MD

Hanusch Hospital of Vienna

Vienna, Austria
Thomas Noesslinger, MD
Michael Pfeilstoecker, MD

Czech Republic**Institute of Hematology**

Prague, Czech Republic
Jaroslav Cermak, MD

University Hospital Olomouc

Olomouc, Czech Republic
Jana Vondrakova, MD

Germany**St. Johannes Hospital**

Duisburg, Germany
Aristoteles Giagounidis, MD

Heinrich-Heine Universitaet

Düsseldorf, Germany
Ulrich Germing, MD

Universitätsklinikum Göttingen

Göttingen, Germany
Detlef Haase, MD

Medical School Muenster

Muenster, Germany
Wolfgang E. Berdel, MD

University Hospital Essen

Essen, Germany
Ulrich Duehresen, MD

Italy**Policlinico Tor Vergata**

Roma, Italy
Sergio Amadori, MD

ASL 4 Prato

Prato, Italy
Angelo DiLeo, MD

IRCCS, Casa Sollievo della Sofferenza

Giovanni Rotando, Italy
Pellegrino Musto, MD

Spain**Hospital Universitario**

Salamanca, Spain
Consuelo Del Canizo, MD

Announcing New Clinical Trials

Name of Institution: Pharmion Corporation**Trial Number: AZA PH GL 2003 CL001****Title of Trial or Description:**

A Multicenter, Randomized, Open-Label, Parallel-Group, Phase 3 Trial of Subcutaneous Azacitidine (Vidaza) Plus Best Supportive Care Versus Conventional Care Regimens Plus Best Supportive Care for the Treatment of Myelodysplastic Syndromes (MDS).

Primary Objective is to determine the effect of azacitidine plus Best Supportive Care, as compared with Conventional Care Regimens plus Best Supportive Care, on survival in MDS patients. This international trial is being conducted in 15 countries and has completed enrollment of 358 patients.

Name of Institution: Pharmion Corporation**Trial Number: AZA PH US 2004 CL003****Title of Trial or Description:**

A Multicenter, Randomized, Open-Label Study Comparing Three Alternative Dosing Regimens of Subcutaneous Azacitidine (Vidaza) Plus Best Supportive Care for the Treatment of Myelodysplastic Syndromes. Also evaluating if response can be maintained with maintenance regimens of 75 mg/m²/day of Azacitidine given for 5 days every 28 days or every 42 days. This US Phase 2 trial is being conducted in approximately 30 centers. Enrollment goal is 144 patients with enrollment ending in February 2007.



MDS Centers of Excellence

Would you like your treatment center to become part of the referral system for MDS patients and be designated as a Center of Excellence? To be recognized as a Center of Excellence, an institution must have the following:

- An established university (or equivalent) program
- Recognized morphologic expertise in MDS
- Available cytogenetics and/or molecular genetics
- Ongoing research, including Institutional Review
- Board-approved clinical trials
- Documentation of peer-reviewed publications in the field
- The ability and intention to register patients in the MDS International Registry database

Please contact the Foundation for further information and an application form for your center.

The following centers have qualified as MDS Centers of Excellence:

UNITED STATES

ALABAMA

University of Alabama at Birmingham Comprehensive Cancer Center
Birmingham, Alabama
Peter Emanuel, MD

ARIZONA

Mayo Clinic Hospital
Phoenix, Arizona
James L. Slack, MD

University of Arizona Arizona Cancer Center
Tucson, Arizona
Daruka Mahadevan, MD, PhD

CALIFORNIA

Cedars-Sinai Medical Center UCLA School of Medicine
Los Angeles, California
H. Phillip Koeffler, MD

City of Hope National Medical Center
Duarte, California
Stephen J. Forman, MD

Stanford University Medical Center
Stanford, California
Peter L. Greenberg, MD

University of Southern California Keck School of Medicine
Los Angeles, California
Allen S. Yang, MD, PhD

FLORIDA

Mayo Clinic
Jacksonville, Florida
Alvaro Moreno-Aspitia, MD

University of South Florida H. Lee Moffitt Cancer Center and Research Institute
Tampa, Florida
Alan F. List, MD

ILLINOIS

Loyola University Chicago Cardinal Bernardin Cancer Center
Maywood, Illinois
Scott E. Smith, MD, PhD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University Feinberg School of Medicine
Chicago, Illinois
Olga Frankfurt, MD

Rush University Medical Center
Chicago, Illinois
Stephanie A. Gregory, MD
Jamile Shammo, MD

University of Chicago Medical Center
Chicago, Illinois
Richard A. Larson, MD

INDIANA

Indiana University Medical Center
Indianapolis, Indiana
Larry Cripe, MD

MARYLAND

Johns Hopkins University School of Medicine
Baltimore, Maryland
Steven D. Gore, MD
Charles S. Hesdorffer, MD

National Heart, Lung, and Blood Institute
Bethesda, Maryland
Elaine Sloan, MD

MASSACHUSETTS

Dana-Farber Cancer Institute
Boston, Massachusetts
Richard M. Stone, MD

Tufts University School of Medicine New England Medical Center
Boston, Massachusetts
Geoffrey Chan, MD

University of Massachusetts Medical Center
Worcester, Massachusetts
Azra Raza, MD

MICHIGAN

Barbara Ann Karmanos Cancer Institute Wayne State University
Detroit, Michigan
Charles A. Schiffer, MD

William Beaumont Hospital Cancer Center
Royal Oak, Michigan
Ishmael Jaiyesimi, MD

MINNESOTA

Mayo Clinic
Rochester, Minnesota
David P. Steensma, MD

MISSOURI

Washington University School of Medicine Siteman Cancer Center
St. Louis, Missouri
John F. DiPersio, MD, PhD

NEBRASKA

University of Nebraska Medical Center
Omaha, Nebraska
Lori Maness, MD

NEW JERSEY

The Cancer Center of Hackensack University Medical Center
Hackensack, New Jersey
Stuart Goldberg, MD

NEW MEXICO

University of New Mexico Health Sciences Center
Albuquerque, New Mexico
Robert Hromas, MD

NEW YORK

Albert Einstein College of Medicine Cancer Center
Bronx, New York
Amit Verma, MD

Memorial Sloan-Kettering Cancer Center
New York, New York
Stephen D. Nimer, MD

Mount Sinai School of Medicine
New York, New York
Lewis R. Silverman, MD

New York Medical College/Westchester Medical Center Zalmen A. Arlin Cancer Center
Valhalla, New York
Karen Seiter, MD

North Shore University Hospital
Manhasset, New York
Steven L. Allen, MD

Roswell Park Cancer Center
Buffalo, New York
Maria R. Baer, MD

University of Rochester Cancer Center
Rochester, New York
John M. Bennett, MD

Weill Medical College of Cornell University New York Presbyterian Hospital
New York, New York
Eric J. Feldman, MD

NORTH CAROLINA

Duke University Medical Center
Durham, North Carolina
Carlos M. deCastro, MD

Wake Forest University School of Medicine Comprehensive Cancer Center
Winston-Salem, North Carolina
Istvan Molnar, MD

OHIO

Cleveland Clinic Foundation Taussig Cancer Center
Cleveland, Ohio
Jaroslawn Maciejewski, MD, PhD

OREGON

Oregon Cancer Center at Oregon Health and Science University
Portland, Oregon
Peter T. Curtin, MD

PENNSYLVANIA

The Western Pennsylvania Cancer Institute
Pittsburgh, Pennsylvania
Richard K. Shaddock, MD
James M. Rossetti, DO

Thomas Jefferson University Kimmel Cancer Center
Philadelphia, Pennsylvania
Emmanuel C. Besa, MD

University of Pennsylvania Cancer Center
Philadelphia, Pennsylvania
Selina Luger, MD

UPMC Cancer Centers University of Pittsburgh Cancer Institute
Pittsburgh, Pennsylvania
Anastasios Raptis, MD

TENNESSEE

St. Jude Children's Research Hospital
Memphis, Tennessee
Gregory Hale, MD

TEXAS

Southwest Regional Cancer Center
Austin, Texas
Richard Helmer, III, MD

University of Texas MD Anderson Cancer Center
Houston, Texas
Elihu H. Estey, MD

University of Texas Southwestern Medical Center Dallas VA Medical Center
Dallas, Texas
Simrit Parmar, MD

WASHINGTON

Fred Hutchinson Cancer Research Center
Seattle, Washington
Joachim Deeg, MD

Seattle Cancer Care Alliance University of Washington
Seattle, Washington
John A. Thompson, MD

WASHINGTON, DC

Georgetown University Hospital Lombardi Comprehensive Cancer Center
Washington, D.C.
Ekatherine Asatiani, MD

WISCONSIN

**Medical College of Wisconsin
Bone Marrow Transplant Program**
Milwaukee, Wisconsin
Parameswaran Hari, MD

**University of Wisconsin
Madison Medical School**
Madison, Wisconsin
Mark B. Juckett, MD

OUTSIDE THE UNITED STATES

AUSTRALIA

**Peter MacCallum Cancer Institute
University of Melbourne**
East Melbourne, Australia
John F. Seymour, MD

**University of Tasmania
Royal Hobart Hospital**
Hobart, Tasmania, Australia
Raymond M. Lowenthal, MD

AUSTRIA

University Hospital of Innsbruck
Innsbruck, Austria
Reinhard Stauder, MD

University of Vienna
Vienna, Austria
Peter Valent, MD

BELGIUM

AZ Sint-Jan AV
Brugge, Belgium
Dominik Selleslag, MD

University Hospital Leuven
Leuven, Belgium
Michel Delforge, MD, PhD

BRAZIL

AC Camargo Hospital – Cancer Center
São Paulo, Brazil
Luiz Fernando Lopes, MD, PhD

Universidade Federal de Ceará
Ceará, Brazil
Fernando Barroso Duarte, MD

CANADA

**Toronto Sunnybrook Regional
Cancer Centre**
Toronto, Ontario, Canada
Richard A. Wells, MD

**University of Toronto
Hospital for Sick Children**
Toronto, Ontario, Canada
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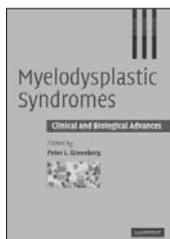
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Myelodysplastic Syndromes: Clinical and Biological Advances

Peter L. Greenberg, MD
Stanford University Medical Center

Hardback

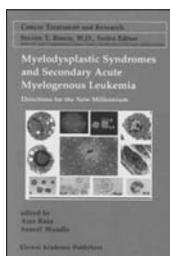
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ISBN: 0521496683/\$125.00**

Cambridge University press

As the current major comprehensive reference on all aspects of the clinical classification underlying pathogenetic mechanisms and treatment of the myelodysplastic syndromes, Myelodysplastic Syndromes stands out as the definitive text on the genetics, pathophysiology, and clinical management of this wide range of syndromes. Authored by international experts, this book provides a state-of-the-art update of the current status and recent advances in the field. The chapters cover all aspects of the myelodysplastic syndromes, from an in-depth analysis of the multifactorial nature of this disease, including a careful assessment of stromal, immunological and stem cell abnormalities, to a review of recent molecular and cytogenetic discoveries and insights.

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Myelodysplastic Syndromes & Secondary Acute Myelogenous Leukemia: Directions for the New Millennium (Cancer Treatment and Research)

Edited by:

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ISBN: 0792373660/\$198.00**

Springer Science + Business Media, Inc.

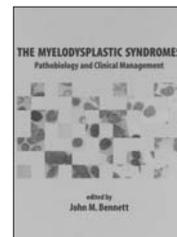
Myelodysplastic syndromes are to the bone marrow what pneumonia is to the lungs; the response of an organ to a variety of etiologic insults like aging, toxic exposure, infections and auto-immunity. Among infectious causes alone, pneumonia could be the result of a variety of possible pathogens including

bacterial, viral, tuberculous or fungal agents. Similarly, MDS cannot be treated as a single disease. Attempts to harness the inherent complexity of MDS by devising “classifications” which group the various syndromes as one disease is as misguided as saying that a pneumonia is not infectious because it did not respond to antibiotics. Progress in the field will occur faster when we re-analyze this premise. Therefore, until a clearer picture of the disease emerges it is best to treat each of the MDS syndromes as a separate entity. Having no classification is better than a misleading one. This book is our attempt to define the most crucial questions related to MDS that need to be addressed immediately through logic, analysis and rigorous experimentation. If the emerging problems appear daunting, then instead of being overwhelmed by them, we should follow the advice of the great 20th century thinker Antonio Gramsci, “pessimism of the intellect must be faced with the optimism of will”.

The Myelodysplastic Syndromes Pathobiology and Clinical Management (Basic and Clinical Oncology Series/27)

Edited by:

John M. Bennett
James P. Wilmot Cancer Center
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May 2002/528 pp., illus.

ISBN: 0-8247-0782-6/\$165.00**

CRC Press. 800-272-7737

This reference provides a comprehensive overview of the latest research detailing the etiology, epidemiology, treatment, and detection of myelodysplastic syndromes (MDS)—identifying effective therapeutic regimens, adverse environmental and genetic factors, and efficient modalities of supportive care that improve patient survival and enhance quality of life.

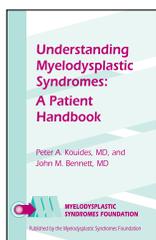
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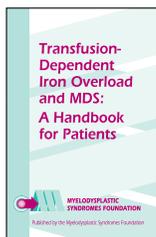
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PATIENT INFORMATION AND EDUCATIONAL MATERIALS AVAILABLE FROM THE MDS FOUNDATION



A. *Understanding Myelodysplastic Syndromes: A Patient Handbook*

Peter A. Kouides, MD;
John M. Bennett, MD



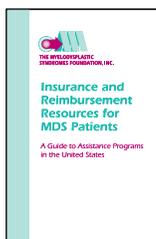
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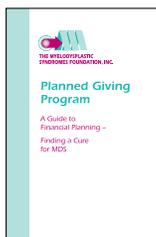
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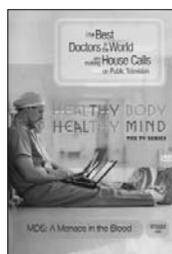


F. *Your Journal: Learning About Myelodysplastic Syndromes (MDS)*

Supported by a grant from
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G. *PBS Program Videotape Healthy Body, Healthy Mind: Learning About Myelodysplastic Syndromes*



H. *PBS Program DVD Healthy Body, Healthy Mind: A Menace in the Blood*

All of these materials are available free of charge from the Foundation.

MDS White Paper Available through The MDS Foundation

This MDS White Paper discusses comparative data and the potential clinical benefits of treatments that are either approved by the U.S. FDA or the EMEA or are under consideration by these bodies. This paper and a subsequent peer-review manuscript will hopefully assist physicians in matching patients with treatment. Coupled with the Foundation's other endeavors we hope to impact the care that is available to patients around the world.

To download your free pdf copy, visit our website www.mds-foundation.org or, if you prefer, call 800-MDS-0839 to request a hard copy.

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The MDS Foundation relies entirely on gifts and membership fees to further its work. We would like to acknowledge the generosity of the following individuals and organizations that have recently provided gifts to the Foundation:

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Susan J. Ferber, In memory of Dr. Jerome Ferber
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If you wish to support the work of the Foundation in the battle against myelodysplastic syndromes, please remember us during the holidays and consider donating a year-end gift. We hope you include us as one of the worthy charities that you support. We have enclosed a pre-addressed contribution envelope to make it easier.

You will also receive an MDS Foundation enamel lapel pin in appreciation of your donation.

All donations are tax-deductible.

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Many families are affected by living with the reality of MDS. There is an extraordinary way to contribute to the MDS Foundation and support our mission of working as a resource for patients, families, and healthcare professionals.

A commitment to donate to the Foundation on occasions of loss, birthdays and anniversary remembrances can be made. Honor your friends or family members on these occasions with a donation, and The MDS Foundation will send an acknowledgment to the recipient, recognizing the occasion.

**A Living Endowment donation
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A fund has been established by the MDS Foundation in memory of Suzanne Fleischman. Contributions may be sent to the Foundation with a notation designating the Suzanne Fleischman Memorial Fund for Patient Advocacy. New donations have been made by:

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