Aplastic Anemia & MDS
INTERNATIONAL FOUNDATION

the MDS Connection

Important Information for People Living with Myelodysplastic Syndromes

ISSUE 11, OCTOBER 2012

Interviews with the Experts – MDS We Don't Often Think About

Specialists Speak about MDS Subtypes Having a Lower Profile

B. Douglas Smith, MD on recurrent and secondary MDS

Dr. Smith is an associate professor of oncology and has been member of the Division of Hematologic Malignancies at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Dr. Smith's clinical interests focus on treating patients with myeloid malignancies, including those with acute myeloid leukemia, chronic myeloid leukemia, and myelodysplasia. His research focuses on developing new therapies to treat these blood and bone marrow cancers. Dr. Smith holds national leadership positions by representing the Sidney Kimmel Comprehensive Cancer Center on the National Comprehensive Cancer Network guideline panels for acute myeloid leukemia (AML) and chronic myelogenous leukemia (CML) as well as participating on the Leukemia Working Group of the Eastern Cooperative Oncology Group.

Recurrent MDS – Why Does It Happen?

Is MDS that returns after treatment(s) have successfully controlled it considered recurrent MDS?

The idea of the recurrent MDS is exactly that. If a patient's MDS has been treated into remission or even controlled and stabilized from an earlier state and then starts to progress with symptoms, worsening blood counts, and worsening bone marrow studies, that is recurrent MDS. Recurrent MDS can happen after supportive approaches, after medical treatments, and even after an allogeneic stem cell transplant. So, I think of recurrent MDS to mean progression or re-emergence of MDS after a period of remission or managed stability.

Connect online with other MDS patients

Find us on Facebook at www.facebook.com/aamds

Patrick Andrew Brown, MD on pediatric MDS

Dr. Brown is an expert in the diagnosis and treatment of cancer in children and young adults. His primary area of expertise is in the area of blood cancers, including leukemia and lymphoma. He is a leader within the international Children's Oncology Group (COG) consortium, serving on the executive steering committees for both acute lymphoblastic leukemia (ALL) and myeloid disorders. He is the principal investigator of active clinical trials for leukemia in COG and in the pediatric oncology experimental consortium (POETIC) and therapeutic advances in childhood cancer (TACL) pediatric phase I consortia, which are investigating novel targeted agents in childhood cancer. He co-chairs the National Comprehensive Cancer Network (NCCN) ALL Panel.

What is pediatric MDS, and why is it seldom mentioned in larger discussion about MDS?

Pediatric MDS, like adult MDS, is a clonal myeloid malignancy that is typically first spotted as cytopenias (low blood counts). It's a stem cell disorder in the bone marrow that results in disturbances in blood cell differentiation and apoptosis (cell death). It is distinguished from acute myeloid leukemias (AML) by having a relatively low percentage of blasts (immature blood cells in the bone marrow). There's really no difference in the definition of MDS as it applies to children or adults – the only thing that makes it a different category is the age of the patient. The reason it's seldom mentioned in overall discussions of MDS is because of a far lower incidence than the adult age group and particularly, the older adult age group. The other interesting point is that within pediatric myeloid malignancies, pediatric MDS is a much smaller proportion than it is for adult myeloid malignances. Less than 5% of pediatric myeloid malignancies are MDS, whereas it's much higher in for adult myeloid malignancies.

continued ▶

Patrick Andrew Brown, MD on pediatric MDS

◀ *continued from cover*

There are several classification systems used for identifying subtypes and their potential severity and risk levels of MDS in the adult patient population. Do these classifications also apply to pediatric MDS?

That's a good question. They can apply and we do our best to apply those classification systems. We have attempted to fit pediatric MDS into the World Health Organization (WHO) classification system, but it's not optimal for this. This is because there are certain subtypes of MDS, for example, refractory anemia with ringed sideroblasts (RARS), that don't occur in children. Another interesting point is that one-third to one-half of children with MDS has an associated constitutional abnormality that can play a large part in the child developing MDS. The most common ones are Down Syndrome and inherited bone marrow failure diseases such as Fanconi Anemia. Those are difficult to classify in the adult systems because they generally don't take inherited abnormalities into account.

Another issue is that familial MDS is not uncommon in children with MDS. Many young MDS patients will have siblings who also have MDS. We have had a few families we have treated with familial monosomy 7-related MDS, and that doesn't occur on the adult side. Finally, some of the subsets of cytogenetic abnormalities that occur in MDS are very different in children. A larger proportion of children have monosomy 7 compared to adults, and a much small proportion of children have the 5q-minus variant – this one is almost never seen in children.

Do the several different treatment approaches (watch and wait, supportive care, active treatment including stem cell transplantation) used in adult MDS apply to pediatric MDS?

They typically don't apply. Our approach on the pediatric side is to take the patient to an allogeneic bone marrow transplant as soon as possible because it's a much different set of circumstances. For younger children, a bone marrow transplant, like adults, is the only potential curative therapy for MDS. Because children are often in a better position to handle the intensity of bone marrow transplant therapy, and because the potential upside of number of years of life that can be extended is much higher, we usually try right away to find a bone marrow transplantation option for a pediatric MDS patient.

Has there been any promising recent research with regard to pediatric MDS?

Because pediatric MDS is so heterogeneous, most of the research occurring is more in the conditions that can predispose to MDS, or make it more likely for pediatric MDS to occur. For example, with Down syndrome-related MDS, there have been striking advances in the understanding of what causes it and the development of different treatments that can help. There have also been advances in understanding the genetic causes of various bone marrow failure syndromes. But those haven't yet translated into better therapies for pediatric MDS once it develops - bone marrow transplant remains the treatment of choice.

What do parents of children diagnosed with pediatric MDS most need to know?

There are two points here. We consider pediatric MDS to be a curable condition as long as a patient can have an allogeneic bone marrow transplant. Just like with recurrent MDS, bone marrow transplantation doesn't guarantee a cure. However, the proportion of pediatric patients for which we can find a suitable donor and who can tolerate a transplant is so high that we can reasonably be very optimistic about pediatric patients diagnosed with MDS.

It's also important to say that any parent of a child diagnosed with a rare blood or bone marrow malignancy like pediatric MDS should be treated at a specialized pediatric oncology center. It should one that has a lot of experience with these conditions and that also has a collaborative relationship with their adult oncology colleagues, who see many more cases of MDS and can be a great source of expertise and advice.

Celgene Corporation Announces Fast Track for First Prescription™— Expedited Fulfillment of First Prescriptions for Patients

CELGENE PATIENT SUPPORT® Fast Track For First Prescription™

As a part of their ongoing commitment to patients, Celgene Corporation announces Fast Track for FirstPrescription™. This is a new opt-in service from Celgene Patient Support® which helps patients on an oral Celgene product receive their first prescription faster.

Which patients are eligible for this service?

- Patients on an oral Celgene product receiving their first prescription for a Celgene medication
- Patients with documented proof of insurance
- Patients who are registered in a Celgene Risk Management (REMS) program and have a valid authorization number

For further information please call Celgene Patient Support® at 1-800-931-8691

There are other variables that are associated with developing MDS, including exposures to toxins or chemicals, and tobacco. These also appear to be important for developing secondary MDS.

Are the factors influencing secondary MDS thought to have different degrees of risk?

As I mentioned, there are certain specific chemotherapies that tend to carry a higher risk of developing secondary MDS. The most common classes of chemotherapies that are associated with MDS are the akylating agents and the topoisomerase-2 inhibitors. While chemotherapy drugs target the cancer cells, they also can damage the DNA of normal cells, and this can eventually give rise to a bone marrow disorder like MDS. There are a couple of well-described forms of therapy-related MDS. One form is rapid onset. This is one to three years following exposure to the cancer treatment, and there's another form that has a longer latency period, maybe four to six years following exposure. The type of treatment people receive for cancer gives you a clue to what type of therapy-related MDS they are experiencing.

It is believed that secondary MDS is harder to treat than de novo MDS. Is there a reason for this?

First, therapy-related MDS does not respond as well to traditional medical management, and the chances of our available therapies to work is lower in secondary MDS. This also includes the success of allogeneic stem cell transplant being lower for these forms of MDS. Therapy-related MDS also tends to act more aggressively than some of the prognostic scoring systems might indicate. Because of this, developing better treatments for patients with therapy-related MDS has become a focal point for many research teams and pharmaceutical companies.

Another point to mention is that in part due to being harder to treat and being more aggressive, the newest MDS classification schemes now refer to treatment related MDS as a form of AML, which is referred to as 'therapy-related myeloid malignancies' even without meeting the traditional 20% bone marrow blast definition. Most feel that this better describes how the disease will behave, aggressively, and many feel that is how the treatment of it should be approached, aggressively.

Apart from avoiding the known risk factors, is there anything people can do to avoid secondary MDS?

Unfortunately, there is not a lot one can do to avoid therapy-related MDS. It is certainly important to understand that there is a risk when starting therapy for a known malignancy. If the best standard approach includes drugs that increase this risk, it is hard to compromise the immediate treatment plan for a theoretical risk of developing MDS.

If chemotherapy is a secondary MDS risk factor and was used for de novo MDS treatment, would this fall into the recurrent or de novo secondary MDS category?

I think that the best way to look at that answer is that if you are using chemotherapy or other medical treatments for a patient's MDS, and they progress, it is not recurrent MDS. If their MDS does respond and then gets worse, it is recurrent, but not specifically therapy-related. Maybe this would be best described as progressing MDS.

How does secondary MDS fit in with the various classification systems that have been developed, especially the International Prognostic Scoring System (IPSS)?

It does not really fit into the IPSS as patients with treatment-related MDS were not included in original IPSS development. There are new classification schemes in development since then, including a prognostic scoring system from the MD Anderson center specially looking at patients who have therapy-related MDS. They use cytogenetic risk and the World Health Organization (WHO) classification to create a point system much like IPSS to place patients into certain risk groups. Similar to the IPSS, this system does suggest that the risk groups have different survivals. In a similar manner, efforts to figure out how to classify pediatric MDS are ongoing as this in another group that was not included in the original development of the IPSS.

Do secondary MDS patients have to approach their disease differently than de novo MDS patients?

Most physicians approach MDS in patients based on their prognostic score, which defines whether they have a high or low-risk disease. It makes sense that each patient should understand exactly what their disease is and how it is expected to behave, and what treatment and support options exist for them. If this is the case, most patients with therapy-related MDS end up falling into the high-risk category either based on number of cytopenias (low blood counts, chromosomal abnormalities, or percentage of blasts in the bone marrow) and historically, we see that therapy-related disease tends to behave aggressively. Our approach, and that of many MDS experts around the world, is to try to match up a treatment plan to give them the best chance for getting their marrow stabilized and then to explore how to keep it stable as long as possible or even move to a treatment that might cure their disease.

Guardians of Hope

"I have included AA&MDSIF in my will because it is my source of information and is presented in a caring way to patients facing MDS."
— Joseph Costa, MDS Patient

Put AA&MDSIF in your will and be recognized among our Guardians of Hope, funding programs and research.

Ask your attorney to include this wording in your will, tailored to your preferences: "I give, devise, bequeath $_____ (amount) or ____% (percentage) to the Aplastic Anemia & MDS International Foundation (AA&MDSIF), 100 Park Avenue, Suite 108, Rockville, MD 20850, a not-for-profit corporation for its charitable uses as directed by its Board of Directors."

B. Douglas Smith, MD on recurrent and secondary MDS

◀ *continued from cover*

Is the frequency of recurrent MDS known, and is a certain type of patient more likely to experience it?

To date, this has not been well studied, but what we do understand is that the large majority of patients with MDS who have periods of disease stability or respond to treatments will eventually recur. Most supportive care or active medical treatments are more temporary treatments and are not permanent or curative.

Is it known why recurrent MDS happens?

The simple answer is that the MDS is a progressive bone marrow failure disorder, and over time, it tends to get worse for most patients. The medical therapies we have do work for many patients, but because they are not curative, their MDS will often become resistant to the treatment. We do know a lot more about MDS than we did just 10 years ago. We understand that there is a series of genetic events (mutations) that occur in the development of MDS and their accumulation can also be associated with the progression or recurrence of the disease. So even when a treatment works for awhile, it is possible that the responding MDS will obtain additional genetic events that render it resistant to the very same treatment. There are certainly many groups working on understanding the development of mutations in hopes of finding better treatments.

Is anything done differently when it comes to treating a recurrent case of MDS?

MDS, like all blood and bone marrow cancers, can go into remission and then recur. Once bone marrow and blood cancers recur, we don't think of them as being curable by medical treatments. So when patients have recurrent or progressive MDS, we often explore the possibility of whether an allogeneic stem cell transplant might be something appropriate for them. Not all patients are good candidates for a stem cell transplant, but many are.

If stem cell transplantation is the only cure for MDS, does that mean recurrent MDS cannot occur in someone who undergone a transplant and no longer has MDS symptoms?

It needs to be stressed that an allogeneic stem cell transplant is not a guaranteed cure. Not all transplants are successful. So, in fact, many patients will have recurrent MDS following a stem cell transplant. Efforts continue to try to lower the chance of MDS returning after a stem cell transplant, but still somewhere between one third and one half of patients will eventually have their MDS return even after a potentially curative stem cell transplantation. So stem cell transplants aren't the answer for all patients or all types of MDS.

What do patients who are post-treatment most need to know about recurrent MDS? Is there anything they can do to lessen the chances of this occurring?

We don't have really good answers here. I strongly encourage all patients and families to play active roles in monitoring their condition and frequently be seen and evaluated by their medical team. Blood cell counts have to be monitored because changes in these are often the first sign of a recurring MDS. Also, they should take the necessary steps improve and maintain their overall health. This means plenty of rest, staying physically active, and working towards a balanced and healthy diet. What we've found through the years is that patients who are in good overall physical health tend to better tolerate different treatments. It is also important to maintain a very active dialog with your physician and treatment team to help manage the disease and to build a solid understanding of what is going on with your body and bone marrow so you are ready to face any changes in your bone marrow that may occur post-treatment.

Secondary MDS – MDS from identifiable external factors.

What is the difference between de novo MDS and secondary MDS?

De novo MDS refers to an MDS that has arisen without an obvious or specific cause. Secondary MDS tend to have two general categories: the first is MDS that seem to have arisen or grown out of another bone marrow failure disorder or bone marrow cancer. For example, there are aplastic anemia patients with very low blood counts, and at times, we see a population of MDS cells that can develop. This may also occur related to other bone marrow problems like having an underlying myeloproliferative disorder with a background of MDS cells as well.

The second definition relates to the MDS being related to previous cancer therapies, including chemotherapy and radiation therapy. So the language we use to describe the secondary MDS types has evolved over time into the "therapy-related MDS" and "MDS arising from or associated with another primary bone marrow disorder." People tend to hear a bit more about the therapy-related MDS.

By what degree is secondary MDS less frequently seen than de novo MDS?

Secondary MDS makes up a small fraction of all the cases of MDS – many studies looking at the frequency suggest 5-15% of the cases are therapy-related.

What are the known risk factors for developing de novo secondary MDS?

The risk factors for therapy-related MDS really relate to the previous therapies that patients have undergone. Certain chemotherapies have a high incidence that are often associated with therapy-related MDS, and of course, radiation exposure is also felt to be a risk factor for developing MDS.

Supported by an unrestricted education grant from Celgene Corporation.

The Patient Perspective

From medical professional to patient: Marie Clark's story of survivorship

An oncology RN's path to a definitive diagnosis

In the spring of 2007, I noticed abnormal bruising. Blood tests showed a low platelet count of 46,000 (normal 150K-450K). My primary care physician quickly sent me to a hematologist near our home in Belmont, New Hampshire. As a registered nurse with a specialty in oncology, I knew this was not good. Needless to say, I was anxious. I was devastated when the hematologist informed me that he suspected it was MDS, a bone marrow failure disease that can progress to leukemia. The hematologist had the initial bone marrow biopsy performed at our local hospital in July 2007.

In the beginning, the most difficult part was waiting for a firm diagnosis. The original bone marrow biopsy performed by my hematologist was inconclusive and did not confirm a diagnosis. As we waited, I began to require transfusions of platelets. Knowing that we were growing impatient and wanted more answers, my hematologist sent me to Dartmouth-Hitchcock Medical Center in Dartmouth, New Hampshire to see a bone marrow disease specialist. With a couple of more bone marrow biopsies, I had my firm diagnosis of MDS by October 2007, four months after becoming symptomatic. I was now receiving both platelets and blood transfusions weekly. My life had changed – I began to think about how much time I would have.

Marie's professional background provides an advantage

As a nurse, I knew the seriousness of my situation. My advantage was that even though I'd never worked with an MDS patient, I understood the disease and the clinical information the doctors were providing. My husband, Kit, who is also a nurse, obtained information and literature from the Aplastic Anemia & MDS International Foundation and scoured the Internet for causes and cures. I was given a trial of high dose prednisone and G-CSF (Neupogen®). Both the prednisone and the G-CSF were started in late November and ended by the first of February. During this time, I continued to receive both platelets and red blood cell transfusions weekly. My hemoglobin levels dropped to less than seven, and my platelets dropped to as low as 8,000. I was completely dependent on someone supplying me with blood each week. It was Christmas 2007. I had a choice: continue with supportive care or find a treatment.

Seeking treatment through clinical trials

My husband pursued clinical trials, and my bone marrow specialist suggested that I consider going to the National Institutes of Health (NIH) in Bethesda, MD. He knew a specialist

there. After coordination and help from my physician at Dartmouth, we had an initial visit on February 5, 2008 to evaluate me for the possibility of a clinical trial. After reviewing my diagnosis, I met with the physician in charge of the trial and was offered enrollment into the treatment protocol. At home and after several weeks of decision making, working with the research nurse, I was scheduled. I arrived there in late March 2008. Having been dependent on blood products twice a week for seven months, I had new hope. This was commonly known at NIH as the "Campath Trial."

For two weeks while at NIH, I received daily infusions of alemtuzumab (Campath®). It would wipe out my immune system which was attacking the bone marrow. The infusion each day would cause a fever, shakes, and other uncomfortable symptoms, but became easier each day. Daily, the research nurse and the clinical director would visit and make me feel that indeed there was hope. After 16 days, many transfusions, labs, and treatments, I was discharged and sent home. I was told that improvements in my blood counts may take from a few months to a year. I was scheduled to return to NIH for 3, 6, 9, and 12 month follow-up exams. My white blood cell count upon discharge was about 0.5 with an absolute neutrophil count (ANC) of 500.

At home again in April 2008, I continued my care at Dartmouth. I received blood and platelets as expected over the next couple of months, but in late June 2008, I did not need the blood. I was making my own! In remission, I see my bone marrow disease specialist at Dartmouth quarterly to follow labs and visit NIH yearly. Next March will be my five-year follow-up visit. To celebrate, I gave myself a new birthday – the day I started the alemtuzumab clinical trial. Now I travel and visit with my grandchildren. Life is good – and I am a *survivor* of MDS.

My sincere thanks to all of the clinical and research staff involved in my care. I am able and capable today thanks to you. Stay involved, pray, and never lose hope.

Learn more about MDS at www.AAMDS.org/Learn

- MDS Treatment: Options and Issues
- Treating Lower-Risk MDS
- Beating Fatigue
- Survivorship
- Living Well with MDS: A Focus on Emotional Health

Aplastic Anemia & MDS
INTERNATIONAL FOUNDATION
100 Park Ave., Suite 108 | Rockville, MD 20850

Fighting Bone Marrow Failure Diseases Through
Patient Support and Research Since 1983
www.AAMDS.org

answers
support &
hope

the MDS Connection

Important information for people living with myelodysplastic syndromes

Aplastic Anemia & MDS International Foundation

www.AAMDS.org – Your best resource for medical and personal perspectives on myelodysplastic syndromes (MDS)

- **Educational materials**
  Read *Your Guide to Understanding MDS*, a free patient guide that explains in plain language what you need to know to understand MDS—why it happens, what to do about it, how to receive your best care—and tips for living well with MDS.

  Also available are *What to Expect from Treatment: A Guide to Understanding FDA-Approved Drug Therapies for Myelodysplastic Syndromes (MDS)* and *Standing Up for Your Health: Self-Advocacy forPatients with Bone Marrow Failure Diseases.*
- **Print and electronic news**
  Stay current with the latest information on areas relevant to MDS through our other newsletters: *Insider* (print) and *eInsider* (electronic).
- **Patient connections**
  Connect in person at a regional Community of Hope event (for more information, please contact crews@aamds.org).
- **Make an online dedication**
  Dedicate a day in honor or memory of a loved one or to celebrate your own life, on our 2012 Calendar of Hope, **www.AAMDS.org/Dedication**.

Connect with us at www.AAMDS.org!

NO INTERNET ACCESS AT HOME?
Internet-connected computers are found in many locations, including:

- Retirement homes
- Public libraries
- Apartment community rooms
- Senior centers

And it's almost certain you know someone (relatives, neighbors, friends) who is connected!

Contact Us

help@aamds.org **(301) 279-7202 or (800) 747-2820**

Help is Here for MDS Patients

FREE PHONE SUPPORT FOR MDS PATIENTS, FAMILIES, AND CAREGIVERS

Do you need to speak with someone directly about myelodysplastic syndromes (MDS)?

Please contact Leigh Clark, our Patient Educator, at (800)747-2820 option 1, or by email at info@aamds.org. Leigh communicates with people all over the world, answering a wide range of questions about MDS, including information on treatment options, clinical trials, financial resources, and more.

PEER SUPPORT NETWORK

Let this AA&MDSIF resource help you!

The Peer Support Network is a national network of trained volunteers, including patients, caregivers, and family members, who offer information, personal experience, coping strategies, problem solving skills and informational resources to people just like themselves. Speaking with a Peer Support Network volunteer is a great way to gather information and receive emotional support from someone whose life has also been affected by bone marrow failure disease.

To connect with a Peer Support Network volunteer, call (800) 747-2820 option 1, and speak with our patient educator, Leigh Clark, who will match you with one of our volunteers. You can also email her at info@aamds.org.