Interviews with the Experts

Resistance to Hypomethylating Agents in the Treatment of MDS

Hetty Carraway, MD, MBA
Staff Physician
Hematologic Oncology and Blood Disorders
Taussig Cancer Center, Cleveland Clinic

Dr. Carraway received her medical degree from the University of Massachusetts, completed internship and residency in the Department of Medicine on the Osler Service at Johns Hopkins Hospital, and completed her Oncology fellowship at Johns Hopkins University School of Medicine. She also obtained her MBA in the Business of Health from the Carey Business School at Johns Hopkins. She is a translational clinical scientist, with a research focus on experimental therapeutics of acute leukemia, including using novel biological agents (such as epigenetic agents) for adults with acute leukemia as well as new approaches to the treatment of refractory acute leukemia.

How common is MDS that is found to be resistant to treatment with the commonly used hypomethylating agents (HMA), azacitidine (Vidaza®), and decitabine (Dacogen®)?

The overall response rate to HMA based therapy is about 40% to 60%. The landscape is changing slightly, particularly with the use of combination therapies, where we are getting closer to 60% to 80% overall response rates for MDS patients in clinical trials. But that still means about 25% or more patients are experiencing no improvement with these agents. This of course applies mostly to higher-risk MDS patients, because we don’t usually treat lower-risk category patients upfront with these agents. However, we have learned that patients that have not responded to HMA-directed therapy (whether they are low or high-risk MDS) have poor outcomes and survival.

What is the difference between MDS that is refractory to hypomethylating agents and recurrent MDS that returns after successful or partially successful treatment? Is there any understanding of why some MDS is initially resistant to these drugs and why other MDS shows an encouraging response at first, but becomes less effective later?

It is important to identify what we mean when use the words ‘refractory’ and ‘resistant’. My view is that there is a difference, and MDS that is refractory to hypomethylating agents means that patients do not respond to the treatment at all no matter how long they have been exposed to the therapy. In that scenario, we often refer to such patients as ‘primary refractory’ patients.

If there has been some response to treatment with a hypomethylating agent with a meaningful benefit (such as transfusion independence) or a larger benefit (like complete remission) with subsequent loss of that response, that is defined as resistant MDS. Biologically, there may be some difference in the MDS that is refractory versus that which initially had a response and then became resistant to treatment. I would say that the biology of refractory MDS dictates that those clinical situations are harder to treat and have worse clinical outcome(s).

Is it known why some MDS is resistant to these two quite similar drugs? Are there instances where one drug fails and the other does not?

We are trying to get a better understanding of this resistance. One of the ways I like approach this is to consider what the mechanisms of action are for the two HMA drugs. Both 5-azacitidine and deoxy-azacitidine are thought to cause reversal of
Resistance to Hypomethylating Agents in the Treatment of MDS

DNA methylation as well as disruption of DNA synthesis by disruption of the dNTP (deoxyribonucleotide triphosphates: dATP, dCTP, dGTP, and dTTP) pool (building blocks of DNA). One difference between the two is that azacitidine is known to preferentially incorporate into RNA, and as a result, it has a direct cytotoxic effect by inhibiting protein synthesis. Both drugs enter the cell and require a special enzyme to cause phosphorylation that results in its activation. For azacitidine, that enzyme is called uridine cytidine kinase (UCK), and for decitabine, it’s called deoxyxycitidine kinase (DCK). So these kinases causing serial phosphorylation are distinct. We have also learned that using high doses of these agents cause direct cytotoxicity and damage, and using lower doses with longer exposure are optimal for the mechanism of reversal of DNA methylation. This reversal of DNA methylation results in gene re-expression (re-expression of genes that suppress tumor growth) and directly results in killing cancer cells.

There are a few ways to envision the mechanisms of resistance to hypomethylating agents (HMA). One is that there is a decreased transport of either drug into the cell. The transporter used for this is a human nucleoside transporter, known as an hNT. If a cancer cell wants to avoid the toxicity of the agent, then it will find a way to mutate the transporter and thus decrease the ability of the agent to get into the cancer cell. Another mechanism of resistance would be inactivation of the drug by disruption of key enzymes needed to activate the drugs when they enter the cell that we mentioned earlier (UCK and DCK). If the cancer cell inactivates that key enzyme (UCK/DCK) needed for drug activation, then the agent won’t be activated and therefore won’t be able to kill the cancer cell.

Cells can also learn how to increase the elimination of the HMA drug. If the cancer cell increases the ability to break down the active HMA by increasing cytidine deaminase (CDA) levels, the cancer cell can decrease its exposure to the drug by directly eliminating it; then the cancer cell has a growth advantage and can avoid the threat from the HMA. There are some researchers that believe there are differences in men and women with regard to CDA activity and that gender affects the likelihood of response to these agents.

Other things to consider are epigenetic mechanisms of resistance. If there’s heavy methylation on the DNA strand, the HMA drug don’t work as well in that setting because it’s so cumbersome and hard to reverse the methylation burden. It is also thought that these agents can work through immune modulation through up-regulation of PD-1, PD-L1, and up-regulation of regulatory T cells. This may come into play, but is still an area of active investigation.

Is there a way to predict what patients may be refractory to treatment with hypomethylating agents?

There’s one group of scientists that hypothesized that a cancer cell harboring mutations to decrease incorporation of HMA into the cells would be most likely to be refractory to therapy. This group went on to examine the expression of genes encoding the nucleoside transporter proteins and metabolizing enzymes involved in the metabolism of 5-azacitidine (5AC) in samples from primary MDS patients and correlated the data with response to 5AC and clinical outcomes.

The researchers wanted to know if the expression of the enzymes that activate azacitidine (UCK1 and UCK2) predicted clinical response(s) to azacitidine. They looked at a cohort of 57 MDS patients, and their data showed there was a higher UCK 1 mRNA expression in those patients who responded to azacitidine, as compared to those patients who did not. They also found that patients with a lower UCK1 expression had a shorter median overall survival than high UCK 1 expression -- 19 months compared to 49 months. This seemed to be a valuable way to evaluate and predict who may have a longer response or improved survival to HMA directed therapy. Confirming this hypothesis in a prospective manner will help support this research and may help us direct therapeutic choices for our future patients.

It would be great to have markers that help us identify which patients are going respond to specific therapies. We need to do more research with regard to this. We currently have tools like the International Prognostic Scoring System (IPSS) and (IPSS-R), which help with the prognosis for a patient with MDS. Mutation status of specific genes is another tool that is coming to the forefront for evaluating patients with MDS. For example, MDS that harbors a p53 mutation has a worse prognosis than those without a p53 mutation.

We are incorporating these molecular tools in prospective studies for our MDS patients so we can better understand prognosis and hopefully better guide treatment selections for our patients.

What follow-up treatments are there for MDS that resists therapy with hypomethylating agents, and does the next type of treatment selected depend on the risk category or classification of the MDS?

We know that for patients who fail treatment with hypomethylating agents (HMA), there aren’t great options at the moment. This is an area of high investigational interest in pharmaceutical research and for many researchers, as it is a current unmet need. The most important thing for these future studies is to accurately define ‘failure with hypomethylating agent’. We have to be able to demonstrate that the first line HMA therapy has not been effective. One important reason is that, as mentioned earlier, we think there are some differences between azacitidine and decitabine.
Treatment Profiles

Treatment with FDA-Approved MDS Drugs

Decitabine (Dacogen®)

Like azacitidine (see January 2014 MDS Connection), decitabine (trade name: Dacogen®, approved by the FDA in May 2006) is a hypomethylating agent that can be used by lower- and higher-risk patients with all subtypes of MDS, though it is most commonly used in higher-risk MDS. It is a type of drug that interacts with the DNA in the genes that are in your cells. Decitabine affects part of a DNA molecule when it is making a copy of itself.

How Decitabine Works

Methylation is a process that acts like a switch to turn off or “silence” genes in certain cells. When certain genes (called “tumor suppressor genes”) are inappropriately turned off by excessive methylation, MDS cells and cancer cells can grow freely. Too much methylation can cause problems. In some MDS patients, it causes genes in some bone marrow cells to be “switched off” incorrectly.

Decitabine is a demethylating agent, also called a hypomethylating or epigenetic drug. This means that it reduces the amount of methylation happening in your body. This keeps the tumor suppressor genes from being switched off when they should be on. When genes in bone marrow stem cells work correctly, the stem cells can grow into healthy blood cells.

How Decitabine is Taken

Decitabine is taken as an intravenous infusion (IV) in a clinic or hospital. IV infusions are the fastest way to deliver decitabine into your body. The IV infusions deliver the medicine directly to your bloodstream, which then carries it throughout your body right away.

Treatment Cycles

The infusion may be given every eight hours for three days. Each infusion takes about three hours. This three-day treatment is usually repeated every six weeks. Most doctors, however, give the shot once per day for five days in a row, repeated every four weeks (28 days). Patients should have at least six treatment cycles (about six months) to see whether they respond.

The number of cycles you receive depends on how you are responding and how you are tolerating the medicine. Some patients respond as early as the second treatment cycle. Others need more than six cycles. The treatment may be continued for as long as the patient continues to benefit.

Decitabine may also lower your blood counts before raising them. Your doctor will test your blood cell counts before each treatment cycle, and maybe between cycles. Many doctors feel that decitabine works just as well as azacitidine to improve blood counts, and both drugs work best in patients with higher-risk MDS.

Side Effects

If you take decitabine, you might get side effects. You may experience:

- Fever
- Nausea
- Cough
- Fatigue
- Dizziness
- Constipation
- Diarrhea
- Chest pain
- Muscle pain

You may feel even worse before you feel better. So it’s important to stick with your treatment to give the medicine a chance to work. Your doctor may ask you to lower your dose or stop taking decitabine for a while to help manage any side effects. If decitabine is improving your health, your doctor will most likely recommend that you keep taking it.

Communities of Hope are volunteer-led local groups, working together with AA&MDSIF staff, which connect patients and families with each other to provide peer support & information exchange, and to raise awareness and support for AA&MDSIF programs.

For additional information, visit www.AAMDS.org/Communities

Connect with us at www.AAMDS.org!

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

- Retirement homes
- Apartment community rooms
- Public libraries
- 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
Frequently Asked Questions

**Treatment**

The *MDS Connection* has answers to common questions about MDS. This answer is provided by Mikkael Sekeres, MD, MS, of the Cleveland Clinic Taussig Cancer Institute.

How is it decided when to start treatment for a patient and what kind of treatment will be used?

When I meet a person with MDS, I have to first verify the diagnosis from my own observations and a pathologist’s report. The next most important step is to determine what type of myelodysplastic syndrome that person has. There are several classification systems in use now, and there are more that are in development that may be in use soon. As complicated as these classification or prognostic systems may be, in general, we categorize MDS as being lower- or higher-risk. Higher-risk means a higher likelihood of the MDS becoming acute leukemia. For higher-risk MDS, we consider it urgent that therapy be started quickly, to prevent this evolution to leukemia from occurring. With lower-risk MDS, on the other hand, the risk that it may evolve to leukemia is comparatively low, and many people do not need any treatment for years.

If someone has lower-risk MDS, we all have to acknowledge that none of the therapies we have at our disposal is curative. The only curative therapy for MDS is a stem cell (or bone marrow) transplant. In general, this therapy is not offered to lower-risk patients because the transplantation risks, including the toxicities involved, far outweigh the risk that a patient will die from lower-risk MDS. Starting any therapy in someone with lower-risk MDS at diagnosis has not been shown to prolong survival. Therefore, with lower-risk MDS, we will not initiate any therapies until we absolutely have to. When it gets to the point that a patient’s quality of life begins to be affected—with major fatigue, losing weight, and feeling bad every day, or if a person’s transfusion dependency increases from less than once per a month to once every week or two, then it is time to start therapy.

**Terms to Know**

Our website, www.AAMDS.org/Glossary/Terms helps you make sense of new words your doctor might use to describe your disease, and its diagnosis or treatment. For this edition of the *MDS Connection*, we define hematopoiesis:

**Hematopoiesis** (hi-mat-ul-pay-EE-suss)

The formation of blood cells in the bone marrow

www.AAMDS.org/Learn

**MDS Webinars and Webcasts**

**MDS: Low and High Risk Diagnosis and Treatment**

Tuesday, July 29, 2014 • 2:00 PM ET

Presented by: Rami Komrokji, MD
Moffitt Cancer Center

This webinar will use a combination of lecture and case studies to present the most current thinking on the treatment of lower and higher-risk MDS.

**Advanced Understanding of MDS: Recent Advances in Understanding the Molecular Pathogenesis of Myelodysplastic Syndromes**

Monday, August 11, 2014 • Time: 2:00 PM ET

Presented by: Laura Michaelis, MD, ABIM
Loyola University Medical Center

This webinar will focus on helping you understand the recent advances in the molecular pathogenesis of MDS. Dr. Michaelis will discuss of diagnostic procedures and prognostic models and how these tools might allow doctors to refine and tailor treatments to each specific MDS patient’s needs in the future.

**Did you know?**

Dr. Gail Roboz gave an excellent presentation at our Philadelphia conference on the diagnosis and treatment of MDS -- and we recorded it just for you! Visit the AA&MDSIF Online Learning Center at www.aamds.org/learn to view Dr. Roboz and other nationally recognized experts provide answers, support, and hope for MDS patients and families.

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
Resistance to Hypomethylating Agents in the Treatment of MDS

continued from page 2

For some patients that remain on HMA therapy but ‘switch agents’ (i.e., from 5AC to DAC), it is very challenging to understand if patients have truly ‘failed’ the first HMA therapy rather than the fact that they simply had continued prolonged exposure to any HMA therapy.

We know that high risk patients have poor outcomes after failing hypomethylating agents, and poor outcomes in the low and intermediate categories have also recently been demonstrated. For those patients, what can we do? Some patients go to a higher dose of HMA therapy, or just switch to the other HMA hoping that using a different kinase pathway (UCK/DCK) will help. Some patients are progressing from MDS to AML, and they move to a more aggressive approach like intensive induction chemotherapy with the hope to get to bone marrow transplant. And for other patients, enrolling onto a clinical trial is available to them and offers a therapy that they would not otherwise have access to.

Clinical trials that focus on novel combinations may be the best options for patients with refractory or relapsed MDS. (i.e.; PD1 inhibitor plus an HMA or single agent PD1 inhibition). All the options should be discussed with each individual patient if appropriate. It is really the patient and his/her physician’s choice to figure out what is best for that patient.

What is most important for patients to remember if hypomethylating therapies aren’t successful?

First, be sure that HMA therapy is really not effective and isn’t working. Be sure that it truly has gotten its best chance, so don’t stop HMA therapy too soon. Hypomethylating agents take a while (four months) to have an effect, but patients want to know right away if it’s working. Patients should stay on the schedules exactly as prescribed and for the full duration -- don’t settle for an educated guess. The mechanism of action of the HMA is different than classic cytotoxic agents that have far fewer rounds of therapy where treatment stops much sooner. Hypomethylating therapy can go on for four, five, or six months before any improvement is seen, and if there’s a clinical response, we keep giving the HMA as long as it working. If we stop too soon, there will likely be relapse. We know that response is less likely and less robust when therapy is restarted a second time. It may work, but not as well -- so it’s really a lost opportunity if you stop your initial treatment early.

MDS Clinical Trials

Should you consider a clinical trial? Ask your doctor or contact the study coordinators for further information. Learn more in the Clinical Trials section of www.AAMDS.org If you are interested in learning more about clinical trials, search for myelodysplastic syndromes studies actively recruiting patients on www.ClinicalTrials.gov. Below is one example of the many open studies for MDS patients in the United States.

<table>
<thead>
<tr>
<th>Title</th>
<th>Study Purpose</th>
<th>Study Coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II INCB024360 Study for Patients With Myelodysplastic Syndromes (MDS)</td>
<td>The primary purpose of this research study is to assess whether the participant’s disease, Myelodysplastic Syndromes (MDS), responds favorably to INCB024360. The study will also evaluate the long-term outcomes of the participant’s disease after they have finished taking INCB024360.</td>
<td>This study is being conducted at the H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida. Contact: Lisa Nardelli 813-745-4731, <a href="mailto:lisa.nardelli@moffitt.org">lisa.nardelli@moffitt.org</a> Please refer to this study by its ClinicalTrials.gov identifier: NCT01822691</td>
</tr>
</tbody>
</table>
2014 Regional Conferences

What attendees are saying...

“Attending this conference, learning from the experts, and most of all meeting others that truly understand what it’s like to have one of these diseases has helped me finally learn to breathe easier!”

“I have been an oncology nurse for 20+ years and have never heard such a good explanation of what MDS is. The AA&MDSIF always brings speakers that the attendees can understand and speak with if they have questions.”

What they’re learning...

In Detroit, July 26th

9 - 10:30 a.m.
MDS: Current Thinking on the Disease, Diagnosis, and Treatment

10:45 a.m. – 12:15 p.m.
New Directions in MDS: What’s on the Horizon?
Both presented by Hetty Carraway, MD, MBA
Taussig Cancer Center, Cleveland Clinic

1:45—2:45 p.m.
Complementary and Alternative Medicine-Fad Diets and Dietary Supplements from A to Z: What Works and What is Worthless?
Presented by Mark A. Moyad, MD, MPH
University of Michigan Medical Center

My name is Martha Sue Porter, and I celebrated my seventy-second birthday on May 7th of this year. I have MDS, and this is my third year as a survivor, having been diagnosed in September 2011.

I have an older son and daughter-in-law who have two young children - my delightful grandchildren and a younger son, Justin, who has chosen to live with me all his life. We share living expenses and enjoy each other’s company.

In 2011, I was so caught up in our family life that I took little notice of several upper respiratory infections that ended in pneumonia. In the hospital I was told my hemoglobin was 8.4 (normal 12 – 16) and was given a blood transfusion and referred to a hematologist/oncologist. At that time I vaguely wondered, “Why an oncologist”? This doctor did a bone marrow biopsy, and it showed I had MDS.
I am one of the lucky ones. I am low-risk, my subtype is RARS (refractory anemia with ring sideroblasts) - anemia with some red blood cells that look like little “Saturns” with rings of iron around them. This subtype is usually low-risk, does not often transform into leukemia, and is slow in its progression. I was started on injections of Aranesp® and after several months was switched to Procrit®.

It was only after much research on the Internet, learning a completely new vocabulary, and attending my first AA&MDSIF patient and family conference that I slowly accepted that I did have a cancer. Educating myself about my disease made me feel less overwhelmed and distraught, and more trusting that there was hope.

In the spring of 2013, I made a difficult decision that my current doctor, a kind, caring and very skilled physician, was not meeting my needs. I had so many unanswered questions about this complex disease. So I found another doctor within driving distance of my home. My younger son went with me to the initial consultation and that doctor sat with us for an hour and answered our questions thoroughly and methodically.

He accepted me as a new patient and after six months of higher doses of Procrit®, I was in what my new doctor termed a “good stable remission” with hemoglobin counts of 9.1 to 9.8 and other blood counts only slightly off normal. He suggested that we approach treatment as “watch and wait” with good supportive care to help manage my symptoms. I’ve felt respected, helped, and supported and know I can call anytime between three month appointments if I don’t feel well and I will be seen sooner.

2013 brought me other challenges that required emotional support. On one of my visits to this doctor, I was told, “Wait five minutes, and I will be back.” Soon the Director of Social Services of the Center appeared at the door with a handful of resources and the experience of many years to help me. She knew about my 34-year career as an addictions counselor and program director. She told me,” You’ve given so much to other people. Now it’s your rainy day, and I’m your umbrella!”

My life has improved from the day of that visit. I have a caring MDS physician. I have a supportive loving son, who drives me everywhere since I am also visually impaired. He is my rock. My family lives close enough that we are often together. I have hope on a daily basis.

I still feel very fatigued two or three times a week, but I am learning ways to deal with that. Sometimes I still grow impatient with the “waiting” of low risk MDS. I still occasionally have down times. I try to help myself everyday by writing in my journal (I have kept a journal for fifty-two years!). I write about what was beautiful, precious and fun about every day. I try to see the daily gifts nature provides us in the changing seasons.

When I feel lonely, I turn to my family, my two best friends, and my foundation. My son described this year’s Philadelphia conference best in these words, “It felt like a huge family reunion, a world of love and caring”.

I wish I could sit down and have a face-to-face chat with everyone who is reading this article. I have been comforted, supported, had my questions answered, and been given hope by so many people who have generously listened to me. I hope some of these things work for all of you.

### HOPE IS SEEN IN THE FUTURE.
Thank you for your consideration!

**AA&MDSIF continues to work toward finding better treatments and cures through research, providing more than $4 million in grants to 67 researchers over the past 25 years.**

**Join us! Make a gift to help advance this vital research.**

Many options are available to create a Named Research Fund: pledge over two or three years, establish with a gift of stock or appreciated securities, or establish through a bequest or estate gift.*

To learn more, please contact the AA&MDSIF Development Office at (301)279-7202 x104 or witt@AAMDS.org

**Research programs include:**

The **Research is Hope Fund** combines the gifts of any amount from families and individuals to fund a two-year research grant of $30,000 per year.

**Names Research Funds** support scientific/medical research projects with a two-year grant of $30,000 per year. Named Research Funds can be created in tribute to a loved one.

*Always rely on your attorney or other qualified advisors to guide you through your estate planning process.

**AA&MDSIF is a 501(c)(3) organization. Federal ID #52-1336903**

Gifts to AA&MDSIF are tax deductible to the fullest extent of the law.

### Thank you for your consideration!
AA&MDSIF - Your best resource for medical and personal perspectives on myelodysplastic syndromes (MDS)

**IN PRINT**

**Fact Sheets**
- AA&MDSIF Social Media
- Bone Marrow and Stem Cell Transplantation**
- Clinical Trials**
- Communities of Hope
- Financial Resources
- How to Evaluate Health Information on the Internet
- Iron Overload
- Online Learning Center

**Patient Guides**
- Your Guide to Understanding MDS*
- Understanding MDS Drug Therapies
- Living Well With Bone Marrow Failure Disease**

* Available in French, German, Italian, Portuguese and Spanish
** Available in Spanish

To order a patient packet, call (301) 279-7202 x116, or order online at www.AAMDS.org/Info.

**ONLINE**

Online Learning Center
www.AAMDS.org/Learn

Learn at your own pace and in the style that suits you best!

**Explore**
- Live and Archived Webinars
- Prerecorded Webcasts
- Video Interviews with Experts
- Interactive Learning Modules

**IN PERSON**

Phone Support for Personal Attention

Contact our patient educator at (800) 747-2820, option 1, or by email at info@aamds.org, for answers on a wide range of questions, including information on treatment options, clinical trials, financial resources, and more.

**Support Connection**

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