Tailored Therapies for Myelodysplastic Syndrome

David Steensma, MD, FACP:

[Slide 1]

Hello, and thank you for joining us for a seminar on “Tailored Therapies for Myelodysplastic Syndromes.” This activity is provided by Vindico Medical Education and supported by an educational grant from Celgene Corporation.

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My name is David Steensma. I am from the Adult Leukemia program at the Dana-Farber Cancer Institute and Harvard Medical School in Boston, Massachusetts. I’m joined today by 2 colleagues who are experts in myelodysplastic syndromes and national leaders in these disorders: Mikkael Sekeres from the leukemia program at Cleveland Clinic and Guillermo Garcia-Manero from the University of Texas MD Anderson Cancer Center.

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Today, we’re going to discuss the importance of risk stratification for treatment selection in MDS; the available treatment strategies for these diseases; management of MDS, both first-line and after first-line therapy fails the patient. And we’re going to begin with Dr. Sekeres and a discussion of the importance of risk stratification in myelodysplastic syndromes. Dr. Sekeres?

Mikkael A. Sekeres, MD, MS:

[Slide 4]

Thank you, David, and thank you, everyone, for tuning in today. I’m going to be talking about, “Anticipating Response to Therapy: The Importance of Risk Stratification in Myelodysplastic Syndromes.”

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I am on an advisory board for Celgene Corporation, which is providing funding for this activity.

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So, myelodysplastic syndromes were really first classified using the French, American, British Classification Scheme, which was a pathologic classification scheme. It was developed in 1976
and then revised in 1982 to what we recognize today. It divides myelodysplastic syndromes into 5 different subtypes: refractory anemia; refractory anemia with ringed sideroblasts; refractory anemia with excess blasts; refractory anemia with excess blasts in transformation; and chronic myelomonocytic leukemia.

For practical purposes, most of us divide myelodysplastic syndromes into patients who have the lower-risk disease or higher-risk disease. If we were to do that using this classification system, we would say that patients who have excess blasts would fall into the higher-risk category, and those patients with chronic myelomonocytic leukemia would fall into an overlap category of myelodysplastic syndromes and myeloproliferative neoplasms, some of whom have lower-risk disease and some of whom have higher-risk disease.

[SLIDE 7]

When we talk about risk, we’re really talking about overall survival. For patients who have excess blasts, the median survival using the French, American, British classification system falls <2 years. For those who don’t have excess blasts, the median survival can be measured anywhere from 3½ up to 8 years. And for those patients who have chronic myelomonocytic leukemia, it falls somewhere in the middle.

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The World Health Organization revised the classification of myelodysplastic syndromes, and the latest iteration of this occurred in 2008. Under this system, the myelodysplastic syndromes are divided into a number of different subtypes, including those patients who have refractory cytopenia with the unilineage dysplasia divided into refractory anemia, refractory neutropenia, and refractory thrombocytopenia; those patients who have refractory anemia with ringed sideroblasts; those patients who have refractory cytopenia with multilineage dysplasia, where multiple cell lines are involved; those patients who have excess blasts – RAEB-1 with 5%-9% blasts, or RAEB-2 with 10%-19% blasts; and those patients who have MDS with the isolated deletion (5q) abnormality; or MDS unclassifiable.

Note that with the World Health Organization, once a patient has 20% blasts, he or she officially has acute myeloid leukemia.

Using the premise that I introduced earlier of lower-versus higher-risk disease focusing specifically on the World Health Organization classification, those patients with excess blasts
would be considered to have higher-risk disease; those patients without excess blasts would be considered to have lower-risk disease.

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Those patients who have RA or RARS have a median survival that approaches 9 or 10 years; those patients with refractory cytopenia with multilineage dysplasia would have a median survival that falls closer to 3 or 4 years; and those patients who have excess blasts, once again, have a median survival that would fall to 2 years or less.

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Now, the International Prognostic Scoring System (IPSS) was published in 1997 based on data on a majority of untreated patients collected in the 1980s and 1990s, and what it does is codifies what’s clinically and intuitively fairly obvious – namely, those patients who do not have a lot of blasts; who have good risk cytogenetics – and in this case “good risk” is considered those patients who have a deletion (5q), deletion (20q), -Y, or normal karyotype; and those patients who have no cytopenias or an isolated cytopenia generally have a good risk disease with a median survival that can be measured 3½ to 5.7 years.

On the other hand, patients who have a high blast percentage who have poor risk cytogenetics – and in this case “poor risk” is defined as those patients who have Chromosome 7 abnormalities or complex cytogenetics of ≥3 abnormalities – and those patients who have multiple cytopenias have a poor survival at a median of 1.2 years or less.

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Now, it turns out myelodysplastic syndromes is not quite that simple. In a revision of Cytogenetic Risk Classification published by Julius Schanz in 2012, now based on approximately 3000 patients, the risk groups were divided into 5 different instead of the 3 different for the IPSS. Now, patients who have a deletion (11q) or -Y abnormality fall into the “very good” category, whereas those patients who have >3 abnormalities in a complex karyotype fall into the worst category.

Patients we previously would have put into the worst category – those with Chromosome 7 abnormalities, or exactly 3 karyotypic abnormalities – along with those patients with Chromosome 3 abnormalities, now fall into the penultimate category of “poor” with a median overall survival of almost 16 months.
This revised Cytogenetics Classification Scheme was used as the backbone for the revised International Prognostic Scoring System. In this system, cytogenetic abnormalities are now given a greater weight than blast percentage, and any patient who has > 10% blasts would get the same score, regardless of whether or not he or she has 11% blasts or 19% blasts. The IPSS-R is more sensitive to the degree of anemia, degree of thrombocytopenia, and uses a neutrophil cut point of 800.

Based on this, patients are given a score and have a median survival that ranges from 8.8 years for those who fall into the “very low” category, all the way down to 0.76 of a year for those patients who fall into the “very high” category.

Also note, the revised IPSS is now based on over 7000 patients, whereas the original was based on slightly over 800 patients.

If we’re trying to simplify all of this, we would put patients who have excess blasts and those who fall into higher-risk categories of the IPSS or IPSS-R into what I would consider to be higher-risk MDS, whereas those patients who don’t have excess blasts or fall into lower risk categories of the IPSS or IPSS-R into a lower-risk category. Please note, I deliberately left off the “intermediate” group in the IPSS-R because we haven’t quite figured whether those patients would fall into a lower or higher risk category.

Now, there are some limitations to both the IPSS and the IPSS-R. One is that they were both developed and validated in patients who really never received any therapy for their myelodysplastic syndromes. They also deliberately excluded patients who had secondary MDS and those patients who had more proliferative types of chronic myelomonocytic leukemia. The MD Anderson Risk Model tries to account for those limitations and is developed based on performance status, age, degree of thrombocytopenia, blast percentage, karyotype, and whether or not a patient is transfusion-dependent. Using this system, patients have a median survival for those who fall into the best risk category of 54 months, all the way down to a median survival of 6
months for those patients who accumulate a score of 9 or greater. This system has been validated using Mayo Clinic data and data from the Moffitt Cancer Center in Tampa.

[SLIDE 16]

Now, within patients who are traditionally thought of as having lower-risk MDS, it turns out that there are some who have truly good disease and those who have disease that more approximates higher-risk MDS. To try to identify these patients, there was another system developed out of MD Anderson that gives point values based on whether or not patients have unfavorable cytogenetics, their age, anemia, degree of thrombocytopenia, and their relative bone marrow blast percentage. Using this system, actually 31% of patients are reclassified as having truly higher-risk disease even though using one of the other prognostic scoring systems, they would have been thought of as having lower-risk disease.

[SLIDE 17]

Now, MDS is even more complicated than that. We've become increasingly sensitive to molecular abnormalities that have been defined within MDS. When those molecular abnormalities are applied to traditional prognostic scoring systems, risk changes.

So, focusing on a limited number of abnormalities such as TP53, ETV6, ASXL1, EZH2, and RUNX1, patients who previously would have been thought of as having an IPSS “low” category would transition up to Intermediate 1; those previously in Intermediate 1 would transition up to Intermediate 2; and those in Intermediate 2 would transition up to the IPSS high risk category if they have one of these specific molecular abnormalities.

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The same is true when these abnormalities are applied to the IPSS-R.

So, in general, one take-home message could be that if patients have one of these poor risk molecular abnormalities, they would be considered as having one step higher risk IPSS or IPSS-R score.

[SLIDE 19]

Now, once again, these systems were developed in untreated patients, and in reality, in our practice, we treat our patients and then we try to risk-stratify our patients after they have received therapy. To attempt to incorporate those molecular lesions into prognostic scoring systems and to
account for these patients who have already been treated and are at various stages of being treated, the Cleveland Group, under the auspices of the MDS Clinical Research Consortium, developed a weighted scale that includes both molecular abnormalities, the IPSS-R score, and age to determine survival in patients regardless of where they are in therapy.

[SLIDE 20]

So, before I mentioned that we consider patients as having lower or higher risk disease. For those with lower risk disease, one treatment algorithm would recommend “watchful waiting” in patients who have limited cytopenias; for those patients who have anemia, to start erythropoiesis-stimulating agents or lenalidomide specifically in those patients who have deletion (5q) abnormalities; for those patients with thrombocytopenia, starting a thrombopoietin agonist or a hypomethylating agent; and for those patients with multiple abnormalities with lower-risk disease, using antithymocyte globulin therapy or a hypomethylating agent.

[SLIDE 21]

For those patients with higher-risk disease, we generally divide them into those who are appropriate for consideration of a hematopoietic cell transplantation, or those who aren’t. In either case, most patients will be started on a hypomethylating agent – either azacitidine or decitabine.

So, one question that remains is, “Are these prognostic scoring systems relevant for patients who are about to receive therapy?”

[SLIDE 22]

Well, it turns out that the IPSS-R has been validated in patients who are about to receive azacitidine by the GFM Group from France, and it does predict survival in a stratified fashion among these higher-risk patients about to receive azacitidine. The system is not predictive, however, of response to azacitidine.

[SLIDE 23]

Similarly, the IPSS-R has been validated in patients with deletion (5q) who are about to receive lenalidomide. Once again, it’s not predictive of response to lenalidomide, but is predictive of overall survival.

[SLIDE 24]
One final note. There are some new drugs that are being used in clinical trials in patients who have failed hypomethylating agents, who have failed either azacitidine or decitabine. The IPSS is frequently used as an entry criterion for whether or not patients receive these drugs.

In another study, through the MDS Clinical Research Consortium, many of these prognostic scoring systems were applied to these patients, and actually none of them has been found to be valid. So, in these patients who failed hypomethylating agents, we need to await development of another prognostic scoring system to determine these patients’ true survival before they enter a new drug on a clinical trial.

[SLIDE 25]
So, I’m going to thank everybody here for listening – everybody from our leukemia and MDS group, and of course our patients.

[SLIDE 26]
Dr. Steensma:
Great! Mikkael, thank you. That was a very engaging presentation.

Increasingly, molecular data are available to clinicians, both at academic medical centers and in the community setting. How do you use molecular data in your practice? Do you just use it for prognostication? Do you use it for diagnosis or for treatment selection?

Dr. Sekeres:
That’s a great question, David. You know, we’re at the beginning of a remarkable era in the understanding of the biology of diseases like myelodysplastic syndromes. Unfortunately for us, our understanding of the biology is moving quicker than the availability of new therapies to take advantage of that new biology.

So, we do send molecular tests on our patients with myelodysplastic syndromes. Sometimes it helps confirm the diagnosis. For example, I recently saw a patient who had a bone marrow with ringed sideroblasts, but not quite enough dysplasia to give further diagnosis of refractory anemia with ringed sideroblasts – one of the myelodysplastic syndrome subgroups. We did send a molecular test, and it did come back positive for a lysosome mutation at SFB31, which we’re increasingly recognizing is becoming a *sine qua non* of refractory anemia with ringed
sideroblasts. So, in her case, I felt more confident giving her a diagnosis of myelodysplastic syndrome than I would have been 5 years ago.

In determining therapy, although we can upstage people using prognostic scoring systems by incorporating molecular abnormalities, in truth, we only have limited therapies available, so we’re still using the same therapies, and at least at our center we are not recommending hematopoietic cell transplantation in patients who would have been considered lower-risk disease using the IPSS or IPSS-R but have been upstaged using these molecular abnormalities.

And the reason is that the data supporting transitioning patients to more of a transplant mode comes from decision models that were based on the IPSS. So, until we have better data supporting the use of these molecular abnormalities to recommend transplantation, we’re still holding off on it.

One cautionary note – and I know you’re well aware of this in an article that we co-authored and that you led – there are patients who are being determined in the setting of mild lab abnormalities to have molecular abnormalities along with them. Some of these patients are being labeled as having myelodysplastic syndrome, or a myeloid disorder.

And there is a cautionary tale to this. The diagnosis of myelodysplastic syndrome still requires pathologic evidence of dysplasia, and in the absence of that, I would continue to monitor these patients off of therapy to see whether or not they do eventually develop dysplasia or more compromise of their blood counts. It may be that these molecular abnormalities that we’re detecting – while they put these patients at increased risk of developing myeloid disorders, they don’t quite make the diagnosis.

**Dr. Steensma:**

Thanks. I have one other question for you, Mikkael. You mentioned a couple of times the MDS Clinical Research Consortium. That’s a new organization that might not be as familiar to some of our listeners. What is the MDS Clinical Research Consortium? What kind of studies does it do?

**Dr. Sekeres:**

So, it’s a consortium that’s funded through the Aplastic Anemia and MDS Foundation via a grant supplied by the Evans Foundation. And it’s a group of 6 institutions, including Cleveland Clinic, Dana-Farber Cancer Institute, Johns Hopkins, the Moffitt Cancer Center in Tampa, MD Anderson, and Cornell, who have agreed to collaborate both in sharing data and conducting clinical trials.
So, it’s a unique mechanism for focusing on these rare collection of disorders, and to focus on even the “rare among the rare” – so, for example, having a clinical trial that’s dedicated just to chronic myelomonocytic leukemia.

Dr. Steensma:

Great. Thank you.

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Dr. Steensma:

So, I’m going to discuss the treatment strategies for the myelodysplastic syndromes as they’re currently used in the clinic. And then Dr. Garcia-Manero is going to talk about emerging therapies and treatments that are being used in clinical trials.

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With respect to disclosure, I have participated in advisory boards for several companies that are sponsors of therapies that are used sometimes for patients with myelodysplastic syndromes. This includes Amgen, Celgene, Eisai, and Novartis; and Genoptix, which is a diagnostic company.

[SLIDE 29]

This figure displays the medications that are currently commonly used for patients with myelodysplastic syndromes. On the left side are those that are approved specifically for MDS-related indications – the 2 DNA methyltransferase inhibitors, azacitidine and decitabine, and the immunomodulatory drug lenalidomide.

In addition, iron chelators, which have a more broad label describing iron chelation in transfusion-dependent patients, are also listed.

On the right are those therapies that are used commonly off-label. For instance, the erythropoiesis-stimulating agents, epoetin and darbepoetin, are commonly used in MDS – in fact, they’re the most commonly used drugs in MDS – but they don’t have a specific FDA label for those indications.

In addition, the myeloid growth factors occasionally see use in MDS, but are generally not effective in terms of preventing infection. They may increase the circulating white cell number, but
those white cells are often dysfunctional and not very good at bactericidal activity, and so these drugs don’t frequently get used in MDS.

Occasionally, patients who are treated with filgrastim or pegfilgrastim will actually have an erythroid response and increase their hemoglobin. That’s particularly true of patients with ringed sideroblasts.

And then finally, on the right side, the growth factor section, romiplostim and eltrombopag, which stimulate production of platelets, are increasingly used for patients with myelodysplastic syndromes, though again they don’t have a specific label for this indication.

Notably, I made a figure similar to this for the first time almost 10 years ago, and the only change that I’ve made is adding those platelet growth factors to it, which highlights, I think, the need for drug development in myelodysplastic syndromes. We really haven’t seen very many new compounds come along in the last decade that have been effective for these diseases.

Uncommonly, immunosuppressive drugs or intensive chemotherapy are used for this condition, and the only potentially curative treatment is allogeneic stem cell transplant; that’s currently employed in only about 3%-5% of patients in the United States – a number that I hope increases in the future.

[SLIDE 30]

Now, this is somewhat of a busy algorithm, but I think what it illustrates is how important the risk assessment that Mikkael just described to you is in determining the most appropriate therapy for a patient with MDS.

For a patient with higher-risk disease, a key decision is whether or not the patient is a stem cell transplant candidate, because if they are, the goal should be to get to stem cell transplant potentially using one of the DNA methyltransferase inhibitors, azacitidine or decitabine, as bridging therapy.

If the patient is not a candidate, then azacitidine or decitabine would be used as long as the patient’s tolerating it until the disease is progressing or relapsing.

If the patient has lower-risk disease, in contrast, then the key questions are, “What is the serum erythropoietin level?” and “If deletion of Chromosome 5q is present?” If the serum epo level is <
500 units/liter, then an erythropoiesis-stimulating agent with or without a myeloid growth factor is appropriate.

If the patient has anemia and del(5q) is present, and they’re either unlikely to respond to epo or have not responded to epo, that’s where lenalidomide comes in.

And finally, the other patients, we don’t always know the best thing to do with – those who are lower risk but are pancytopenic. The optimal approach in those patients is unclear. One could consider a combination growth factor approach or a hypomethylating agent or immunosuppressive therapy. This is a group for which clinical trials are particularly important, as are clinical trials important also for second-line therapy for patients with higher risk disease after a hypomethylating agent has failed.

[SLIDE 31]

We can predict ahead of time which patients are most likely to respond to erythropoiesis-stimulating agents – those who have a lower serum epo level – especially less than 100 – and those who are not heavily transfusion-dependent.

[SLIDE 32]

We can also predict, similarly, which patients are more likely to respond to romiplostim, those who are not platelet transfusion-dependent, and those who have a low TPO level. TPO assays are not as widely available, but Dr. Sekeres did validate this algorithm in predicting which patients with MDS-associated thrombocytopenia are likely to respond to romiplostim.

These data are from a clinical trial in lower-risk MDS of romiplostim versus placebo. Of note, platelet elevation was common in the romiplostim group, and sustained, and this led to a reduction in the number of platelet transfusions used as well as clinically significant bleeding events.

One concern around this drug is that there may be potential to increase the proliferation of the blast population. Sometimes blasts have active thrombopoietin receptors. Romiplostim works by stimulating the thrombopoietin receptor, and so it’s possible that the blast proportion could increase, and that indeed did happen with some patients on this study, leading to premature closure by the Data Safety Monitoring Committee.
Therefore, if romiplostim is used in MDS, it should probably be used only in patients who have been adequately counseled about that risk, and primarily in patients with lower risk disease who don’t already have a blast increase. Again, this is an off-label use.

[SLIDE 33]

Now, an on-label use of lenalidomide in patients with del(5q). Two-thirds of these patients become transfusion-independent, and almost half of them have a cytogenetic response. However, this agent is not curative, and the stem cells with 5q deletion do persist – but again, provide palliative benefit.

Now some patients without del(5q) do also benefit from lenalidomide. About 1/4 of them become transfusion-independent, but that transfusion independence duration is not as lengthy as in the del(5q) population.

And in addition, the patients who have severe thrombocytopenia tend not to respond to lenalidomide, and those with very complex karyotypes also are less likely to respond. So, that may be useful for helping select which patients lenalidomide could be considered for in the non-del(5q) population. Again, that’s an off-label use.

[SLIDE 34]

Now, one of the most challenging therapies with respect to patient selection is immunosuppressive therapy. We do know that, just as in aplastic anemia, suppression of hematopoiesis by an expanded cytotoxic T-lymphocyte clone is present in some patients with MDS, and contributes to the marrow failure. Unfortunately, we don’t have good ways of choosing who those patients are. Patients who have a PNH clone; those who are younger and have a normal karyotype; those who have HLA DRB15; and potentially those who have a hypoplastic marrow may be more likely to respond to anti-T-cell immunotherapy, but none of these predictive models are very strong. This is an area where we need a better understanding of which patients are going to respond.

The anti-T-cell therapies that are most commonly used include antithymocyte globulin and the calcineurin inhibitors cyclosporine or tacrolimus.

[SLIDE 35]
The only drug therapy that's been shown to improve survival compared with supportive care in a subgroup of patients with MDS is azacitidine, which, in patients with higher-risk MDS, was compared to best supportive care, and in a small subset of patients low-dose cytarabine or induction chemotherapy with an AML regimen 3 and 7.

In the patients who received azacitidine, the median survival was about 9 months longer than in those who received one of the control arms.

Mikkael has published data from a large registry that suggest that the effectiveness of azacitidine is comparable whether it's used subcutaneously or intravenously. There's a trade-off here with IV therapy; of course, the patient has to fiddle with IVs and have a line put in. With subcutaneous therapy, the risk of an injection-site reaction is higher, but the patient may be able to get in and out of the clinic more quickly with subcutaneous administration. So, those are the considerations.

The standard schedule for azacitidine is 7 days every 4 weeks.

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Now, as mentioned, stem cell transplant is the only curative therapy for patients with MDS, but only about 800 patients per year undergo allogeneic transplant in the U.S. compared to an incidence of MDS that probably exceeds 30,000.

Allogeneic stem cell transplant is typically reserved for those with IPSS Intermediate 2 and high disease, but we don’t know what to do with the IPSS-R intermediate-risk group, as Mikkael indicated, and this is a group where perhaps molecular testing may help us identify optimal patients for stem cell transplant.

About 40%-50% of the patients who do undergo transplant are cured of the disease. But, in many of the remainder, the disease will recur. At least with reduced-intensity conditioning, the rate of death from complications of transplant is now down below 25%; however, many patients who survive do have chronic morbid conditions such as graft versus host disease that negatively influenced their lifestyle.

Patients who go to transplant who have therapy-related MDS, excess blasts, complex karyotype or especially a TP53 mutation tend to do more poorly.

[SLIDE 37]
Now, red cell transfusion dependence, we’ve known for some years, is a risk factor for poorer outcomes in patients with MDS. Transfusions themselves have a negative effect. In addition, transfusions probably mark patients who have more severe disease.

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One of the interesting and controversial areas in transfusion therapy with myelodysplastic syndromes relates to iron overload. There’s a lot of controversy about the magnitude of risk from transfusional iron overload in these patients. Certainly in patients with excess blasts or a complex karyotype, iron is really a distracter. Those patients have considerable risk of death from progression of leukemia, infection, bleeding, and iron is a more minor component. But for the lower-risk patients who have a relatively good life expectancy and who may be regularly receiving transfusions, iron is a consideration, and chelation therapy can be selected for some of these patients on an individual basis.

We know, for instance, that ferritin levels – at least for lower-risk disease – correlate with poorer outcomes in MDS if they’re elevated, and that the higher they are the worse the outcome. This is also true for patients going on to get stem cell transplant.

Now, ferritin is a kind of a crummy assessment of total body iron stores, so there are other techniques for measuring iron noninvasively, such as T2* or R2* MRI of the liver and heart. We’re just learning how to incorporate them into therapy.

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Patients, importantly, develop iron overload at varying rates. For instance, those who have a polymorphism in the HFE gene would be likely to develop iron overload more quickly than those who don’t have them. There have been a number of studies that indicate that chelated patients do better than those who aren’t chelated, but these have all been retrospective studies or other designs that were subject to selection bias, and the available chelators are problematic. Deferasirox is expensive, and in 2 studies – Phase 2 studies – the dropout rate was about 50% in the first year.

In contrast, injectable deferoxamine is inconvenient for patients as it has to be given 5-7 evenings out of the week in order to have any sort of utility.

And there are no randomized prospective data yet that show a benefit from chelation in terms of morbidity or mortality in MDS, but those studies are ongoing.
So, that sums up some of the current treatment patterns in myelodysplastic syndromes.

Dr. Steensma:

Mikkael, what do you see as the biggest unmet needs in the treatment of patients with myelodysplastic syndrome?

Dr. Sekeres:

Well, I think for lower-risk disease, there is what I would consider to be the next regulatory frontier, and that is in patients who have failed one line of therapy, and we could define that as patients who have failed erythropoiesis-stimulating agents, or we could define it as lower-risk patients who have failed either one of the hypomethylating agents – azacitidine or decitabine – or lenalidomide.

One of the challenges with MDS is that we really only have 3 agents that are specifically approved for MDS, and then we beg, borrow and steal to use other agents approved for other indications where we use them off-label. One example of that, of course, are the erythropoiesis-stimulating agents, and they are the most commonly used drug in MDS. The other would be immunosuppressive drugs such as antithymocyte globulin. So, once patients have failed those drugs, they have little recourse.

For those who are particularly lower risk and maybe just have an isolated anemia who have failed erythropoiesis-stimulating agents, lenalidomide can be tried and, as you’ve shown in the off-label indication of the non-deletion(5q) patients, the response rate is consistently 26% or 27% across 2 studies. But it isn’t durable. In the Santini study (Santini V, et al, ASH 2014. Paper 409) it was 30-35 weeks; in the Raza study (Raza A, et al. Blood. 2008;111:86-93.) their response duration was 42 weeks.

So, these patients are going to need something else, and I think a lot of them are told by their treating doctors, “Well, we’ll just have to go back to giving you transfusions.”

So, there are drugs that are looking at this indication, but so far we haven’t had any one that has been a particular superstar. I think we’re all hopeful about the drugs sotatercept and luspatercept,
both of which are TGF-beta inhibitors, but we’re still waiting on durability of response to those drugs.

**Dr. Steensma:**

Great. Thanks.

**Dr. Sekeres:**

So, David, you talked about lower-risk patients who have multiple cytopenias. I always find them particularly tricky to treat. What are your indications for using ATG or some, like, immunosuppressant in these patients? And then, which of the hypomethylating agents do you consider using in them?

**Dr. Steensma:**

You know, I think the lower-risk patients, as you describe them, are a particularly difficult group. I tend to use the immunosuppressive therapy for those patients who have either a normal karyotype or trisomy 8 – those whose cytopenias are bad enough to warrant therapy, and those who I think are likely to tolerate the therapy. ATG in particular is not a benign therapy.

And so, sometimes for older patients where there aren’t other good options, we might use just cyclosporine or tacrolimus instead. But it is a difficult group to know just how to select immunosuppressive therapy for.

I don’t routinely measure HLADRB15 because that’s quite common in the MDS population generally; it’s overrepresented, and it doesn’t seem to be a strong marker of response to immunosuppressive therapy. So, I usually make that decision on other grounds.

As far as using hypomethylating agents, I do consider doing that in lower risk patients, especially if they’ve become transfusion-dependent, or if their cytopenias are severe enough that I’m quite concerned about them – for instance, a patient whose neutrophil count is consistently below 500 per m$^3$.

The benefit of hypomethylating agents in this population is a little bit unclear. Some patients do have really nice increases in their peripheral blood counts, but we saw some data last year from a Korean group that compared patients who got hypomethylating agents with those who didn’t, and tried to match them using a statistical technique, and found that those who got hypomethylating agents actually had a shorter survival – which certainly gave us pause.
Now, that’s one study, and it was not a prospective trial, but it is something that I think we need to be a little bit careful about in the lower-risk population.

Now, as far as azacitidine versus decitabine, I didn’t say very much about decitabine, but I do use it in my practice; it tends to work a little bit more quickly than azacitidine does. We see responses with decitabine if we’re going to see them generally after 2 or 3 cycles rather than 3, 4, or 5 with azacitidine. But that comes at the expense of what seems to be a little bit more myelosuppression, perhaps a little bit more fevers and neutropenia.

There’s never been a study that showed a survival advantage with decitabine like there is with azacitidine, but that may be just due to either study design or selection of patients that went in. Because if one looks at the control groups of the decitabine-treated patients in the survival studies that were done, they had a much lower survival – 8 months, 9 months – compared to the 15 months in the AZA-001 study.

So, these were clearly looking at different groups of patients.

It’s also possible decitabine and azacitidine are just different and have different degrees of benefit, but my guess is the lack of a comparable survival benefit is just as much attributable to the way the studies were done.

[SLIDE 42]

Dr. Steensma:

And Dr. Garcia-Manero will now tell us about some of the compounds in development and some of the ongoing clinical trials for these diseases.

Guillermo Garcia-Manero, MD:

So, thank you for the opportunity. I’m going to now continue with a review of the management of MDS following first-line therapy failure. My name is Guillermo Garcia-Manero. I’m a professor at the University of Texas, MD Anderson Cancer Center in the Leukemia Department.

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I don’t have any disclosures to present in this presentation.

[SLIDE 44]
So, the first thing to really emphasize is that when we talk about hypomethylating failure, or HMA failure, we’re really separating patients into what we call a “low-risk category failure” or a “high-risk category failure,” and we still use IPSS type of criteria to separate the lower from the higher-risk failure. And this is important because the natural history of these patients is different.

So, in the first slide that I’m going to be presenting, I’m going to show you what is the natural history of patients with low-risk MDS in HMA failure. This was a presentation at ASH couple of years ago that was recently published in the *Journal of Cancer*.

[SLIDE 45 ]

So, this is a study – an analysis performed in the context of the MDS North American Consortium with Dr. Sekeres and Dr. Steensma. And basically we had the opportunity to evaluate the natural history of close to 440 patients with lower-risk MDS at the time of HMA failure; and evaluate not only their survival, but their response criteria based on IWG characteristics.

[SLIDE 46]

And basically, what we learned from this analysis is that the survival of patients with lower-risk MDS in failure – so basically, they’re failing the HMA compound but they are still in a low or intermediate-1 category by IPSS. It’s around 15-17 months as you can see in this Kaplan-Meier plot.

So, survival is not extremely poor, but it’s associated with limited survival for this group of patients.

[SLIDE 47]

The next question that we wanted to address was outcome or impact of any form of therapy in this group of patients. And as you see in this slide, no therapy of course was not associated with any response; conventional therapy – meaning probably some form of RRC type of treatment was associated with response in around 18% of the patients; the same thing for investigational-type of approaches; and the best outcome was basically in those patients that we see for stem cell transplantation, although it was a small number of patients.

So, if a patient is a candidate for a stem cell transplant in lower-risk disease, this would be a situation where I think would be really the most effective form of therapy, and probably the only curative approach for these patients.
We don’t understand the mechanisms of resistance, and of course we don’t understand why patients will fail in a higher- versus lower-risk category. Some patients go into a more proliferative state, where other patients go into a bone marrow situation. But there are a number of groups trying to elucidate this process. For instance, we and others have found that this activation of innate immunity signaling in patients with HMA failure – particularly in the lower-risk stage – this involves activation of NFkB, and potentially kinases like P38 MAP kinase and the PD-1/PD-L1 axis. This is somehow summarized in the slide, and I would refer you, if you are interested on this topic, to the paper cited at the bottom of the slide.

We have used a number of compounds trying to target this pathway – kinases – kinase inhibitors like ARRY-614 or oral rigosertib, although the final results of these trials are not promising enough to take them into more definitive type of trials.

In the next slide, I show you a list of studies that we’re performing at MD Anderson trying to target this pathway. So, for instance, this includes a compound known as “OPN-305” – this is a toll-like receptor 2 inhibitor; MEDI4736 is a PD-1 inhibitor; and then the others basically look at either inhibiting NFkB pathway or trying to block similar pathway[s] with the JAK2 inhibitor ruxolitinib. But these are early trials and we don’t really have a lot of clinical evidence that they are significantly active in this context at this point.

After defining the lower-risk situation, I would like to go into more detail in the higher-risk HMA failure.

This is a complex process; this is where probably a large majority of the patients with MDS stay at the time of failure, and the natural history of these patients, as you can see in this slide, is extremely poor. So, as it was defined almost 5-6 years ago, once these patients with higher-risk MDS failed the hypomethylating agent, their survival is around 4-6 months; and this data first presented by our group in 2010 has been now validated by a number of centers all over the world.
So, again, we don’t understand the mechanism of resistance, but this is a difficult situation and we don’t really have any drug approved for these patients at this point, and I believe that most of these patients should be considered for an investigational clinical trial.

Now, having said that, there is also a significant effort in trying to overcome this resistance, or at least develop new therapeutic agents for these patients.

[SLIDE 52]

So, at ASH this year, data was presented from the first Phase 3 trial ever conducted for this group of patients, and this was a randomized trial comparing basically best supportive care versus a compound known as “ON 01910,” or rigosertib. This is the intravenous form of rigosertib.

So, again, this was the first trial ever conducted for this indication. This is a drug that is given as a continuous infusion daily for 3 days intravenously. This was a study trying to define the impact of this compound on survival, and there were basically 300 patients treated with a 2:1 randomization type of approach, with 199 patients on the rigosertib arm.

[SLIDE 53]

In terms of efficacy, again, the study was powered for survival, and as you can see in the slide that there was a trend toward superior survival with the rigosertib arm – around 8 months – compared to 6 months in the best supportive care.

[SLIDE 54]

Unfortunately, as you will see in the next slide below, this did not meet statistical significance, actually mainly because the curves cross around at 20 months or so. Before that, they seem to be separated. So, the hazard ratio was 0.87, but the $P$-value was not significant. So the study actually failed to show significant improvement in survival.

[SLIDE 55]

But what was interesting is that in pre-defined analysis on this trial, we learned actually that perhaps different groups of patients behave in different ways in terms of their survival with this compound.
And one thing that was striking that is shown here on this slide was that there was a specific subset of patients with very poor-risk features like Monosomy 7, or very high-risk disease by IPSS-R, that seemed to do better with rigosertib compared to the standard of care.

And, therefore, actually, we looked into a little bit of detail into this issue of what we now refer to as “primary versus secondary HMA failure.” So, primary failure is the one that never responds to therapy; a secondary failure – meaning the HMA – a secondary failure is the one that had a response to the hypomethylating agent that was subsequently lost. And what was very interesting, actually, is that rigosertib seemed to have better impact on patients that were refractory or had primary HMA failure compared to patients that had responded already to the hypomethylating agent, and this was actually confirmed by an independent analysis.

[SLIDE 56]

And the slide actually shows you the impact of rigosertib on survival in patients with a primary failure compared to best supportive care, and as you can see there, survival with rigosertib was almost 9 months, where it was 4.5 months with best supportive care. The $P$-value here is significant, and the hazard ratio is around 0.6

Again, this was not a predefined certification criterion on the trial, so we couldn’t use this to basically have this drug approved for our patients. But it’s data that is strong enough actually that has led to the development of a secondary Phase 3 trial with rigosertib that is starting actually around September of this year, targeting this very specific group of patients with primary failure and higher-risk features.

It’s clear also to say that we didn’t see any impact on survival with rigosertib in patients with secondary failure at this point. Why this is the case, we don’t really understand, but the natural history seems to be very different.

[SLIDE 57]

And then, another study that was recently presented was a trial using more conventional chemotherapy with very low-dose clofarabine and low-dose cytarabine, also for the treatment of these patients. As you very well know, clofarabine is a compound used in ALL and has been studied in multiple trials of AML and MDS, but we hypothesized that a lower-dose scale of this compound could have activity in this group of patients with hypomethylating failure.
So, we’ve almost completed the study of 80 patients with HMA failure, most of them with high-risk disease.

[SLIDE 58]

And the data that was presented at ASH last year showed actually a response rate a little bit over 40%. This compound, even if it’s a low dose – meaning 10-15 mg/m² – could have some toxicities in terms of tumor lysis and some kidney toxicities. But, we’re starting to see actually trends in survival that actually may be a little bit better than expected, although this was a single-arm non-randomized trial.

[SLIDE 59]

And what was intriguing actually is that it appeared that there was a group of patients that had very significant benefit that were those patients with diploid characteristics, and indeed actually by multivariate analysis that was the subset of patients that benefitted the most from this therapy.

So, again, this is a compound or a combination that is not approved for this group of patients, but in a specific subset of patients with normal chromosomes, HMA failure with high-risk disease – meaning excess blasts – this could be a potentially acceptable salvage type of approach for a group of patients that otherwise don’t have any other therapeutic alternative.

[SLIDE 60]

Now, there are other compounds that are being investigated. One of them, for instance, is sapacitabine. This is an oral nucleoside analog with some Topo-1 activity. The study actually is being tested right now in a big AML study worldwide. But there’s some data performed from a multicenter clinical trial that indicates also that it’s possible that this compound, that is oral, could have actually an impact on survival in this group of patients with HMA failures, actually with an acceptable toxicity profile. So, the median survival of patients treated with sapacitabine in prior studies was around 8-9 months, so we would like to see actually this compound also being tested in a secondary Phase 3 study specific for HMA failures, but that study actually has not been designed as of yet.

The next question is, “Can you actually a secondary hypomethylating agent for these patients that have failed azacitidine or decitabine. In practice, actually, this is done all the time, so if the patient is on azacitidine they will go and move to decitabine, or vice-versa, for secondary type of therapy.
So, SGI-110 is a second-generation hypomethylating agent. It’s a dinucleotide form of decitabine, so at least in vitro it’s a more potent drug. And this compound now has been tested also in front-line acute myelogenous leukemia and also myelodysplastic syndrome.

But at ASH last year, interestingly, there was data showing actually that it was possible that in a subset of patients with HMA failure, you could rescue a percentage of patients with this compound, suggesting actually that they may not be identical to either decitabine or azacitidine, and this is also being tested in clinical trials.

Perhaps one of the things that we are at least conceptually more excited about in this field is targeting this PD-1/PD-L1 axis. I’m sure that many of you are medical oncologists as well, and you’re using these compounds for melanoma and so forth. But there is data from multiple groups now, including this paper in this slide, that indicate that MDS CD34-positive cells express PD-1 and PD-L1, and further data actually does suggest that treating these cells with a hypomethylating agent like azacitidine may enhance the expression of the PD-1/PD-L1. And with that in mind, there are a number of clinical trials using either single-agent PD-1/PD-L1 inhibitors or in combination with hypomethylating agents that are being developed and starting in multiple centers in North America. And this could be a very attractive approach, both for front-line MDS and of course for the hypomethylating failure group of patients, where a sequential approach of hypomethylating agents with a PD-1/PD-L1 inhibitor would be very attractive.

Of course, I’m not suggesting that you do this off-protocol. These drugs are extremely expensive, and we actually do not understand what the toxicity profile of these new checkpoint inhibitors will be in the context of combination with hypomethylating agent, but I think these are very important clinical trials.

Another phenomenon – and perhaps this is a little trick that I would like to share with you – is that there is now ample data to suggest that a group of patients with myelodysplastic syndrome – when they lose their response or they transform to AMA, they actually may acquire mutations on the FLT3 gene or RAS. Now, you’re very familiar with FLT3 because this is an important gene in
AML, but there is data to suggest that even if at baseline FLT3 mutational status is relatively low, in around 20%-30% of the patients do we see a mutation of RAS or FLT3, and these are things that you could potentially target on a clinical trial—we are thinking in terms of RTP or some inhibitor of the RAS/MAP kinase pathway.

[SLIDE 65]

And indeed actually, this is illustrated on this paper by Dr. Ravandi, where he showed the reports of combination of azacitidine + sorafenib, a potent FLT3 inhibitor. He showed actually a response rate of over 40% in this group of patients, and most importantly, anecdotal experience from this clinical trial indicated that if you added back sorafenib to patients failing azacitidine with a FLT3 mutation, you could go on and rescue that patient with a prolonged response. And I think this is something very interesting in terms of the biology of the disease.

[SLIDE 66]

And to close, I would like to basically just briefly mention 2 of the compounds that I think are probably most exciting, and that I would like to see in our patients in some form of clinical trial in the next, hopefully, few months.

[SLIDE 67]

One of them is AG-221. This is an IDH2 inhibitor. These are mutations that happen not at a very high frequency in MDS, but they occur in probably around 5%-10% of the patients, and this would be an ideal approach for patients with HMA failure if they carry these kind of mutations. This is an inhibitor for IDH1. And this is an important concept because also it affects deregulation of the genetic pathways in this group of patients.

[SLIDE 68]

And the other compound that I would like to see in our clinical trials in patients with MDS is this drug known as “ABT-199” or “venetoclax.” I think this drug probably will be very easy to access at some point due to the activity that was seen in patients with CLL and so forth. But the compound has significant activity in AML, and potentially in high-risk MDS, and there is no reason to believe that this will not be actually a potent approach as well for patients with HMA failure in a high-risk situation.

And with that, I would like to close, and again, thank you very much for this opportunity.
Dr. Steensma:

Guillermo, thank you for that excellent overview of some of the developmental therapies for MDS. One of the challenges that we face in myelodysplastic syndromes is that although there are uncommon mutations like IDH2 that seem to be able to be targeted with agents in development, many of the mutations like splicing and some of the epigenetic mutations and chromatin remodeling, transcription factors, it’s hard to think about how to target them with compounds.

How can we move forward with coming up with therapies to address some of these other more difficult mutations that are not tyrosine kinases?

Dr. Garcia-Manero:

This is a very important issue. The first question is that actually – I think that little by little our armamentarium – at least in a clinical trials – is starting to gain a little bit of space in the percentage of patients, because, for instance, if you screen now for an HMA failure for FLT3/RAS/IDH1/IDH2, our numbers suggest that maybe almost 1/3 of the patients will be informative and could be potential candidates for such a study.

So, I think it’s important that if you have such a patient that you have the opportunity to do this kind of analysis – because it may give an opportunity for differential therapy in a small but not insignificant subset of patients.

Now, you mentioned something that I didn’t talk in the presentation because we don’t have a lot of data yet, and you’re leading some of the studies. But it obvious that one of the most important pathways – particularly in lower-risk disease – is the splicing pathway, and the multiple genes that are mutated and affect this process. And there are a number of drugs that inhibit at least a couple of these mutations that could be, at least academically, effective in this context.

So, I think this is a very attractive approach and a novel indication – you know, different than this kinase type of inhibitory process – but we are not there yet in terms of the clinical trial development, but as you know, you are leading this – we should have hopefully some of these studies hopefully in less than a year, and this will be a very important topic.

I don’t know if we know much about how the splicing pathway is affected in these patients with HMA failure, but that’s an interesting concept.
Of course, some of the other mutations like PET2, DNT3, etc., they probably are present at baseline, and there’s some data to indicate that maybe hypomethylating agents may have differential activity at that point, but we don’t really understand much at the time of failure. So you’re right – those are much more complex.

But today, actually, there are a number of centers in the U.S. that have access to inhibitors of a group of 4-5 mutations that could affect around 1/3 of our patients, and I think that’s a good start.

**Dr. Steensma:**

The other question I had is, in myelodysplastic syndromes we typically use monotherapy. And in most other diseases things are evolving towards combination therapy. So far, our trials of combination therapy in MDS have been somewhat disappointing. Most of the histone deacetylase inhibitor combinations have not been better than azacitidine alone. Are there other combinations that are particularly worth pursuing?

**Dr. Garcia-Manero:**

Well, this is a very dear question to me, and a frustrating one. So, for years, we’ve been working very hard on this combination with Hdac inhibitors and hypomethylating agents. And, for instance, most recently we felt that perhaps a compound known as pracinostat could have a differential effect, and we just learned from initial results from a randomized blinded test study showing actually no effect.

We know the data from the SOAKTRATI study run by Dr. Sekeres, basically with the same type of concept.

So, I think it’s going to be difficult to develop these Hdac inhibitors in MDS anymore, and perhaps it’s because we don’t understand the subset of patients that benefit the most, or maybe there are some issues with the toxicities of these compounds that make it difficult in terms of providing prolonged therapy.

Another combination that has been developed and that we’re not sure what’s going to happen with is actually the combination of azacitidine and lenalidomide. So, again, Dr. Sekeres presented very exciting data a number of years ago. We just published a paper suggesting actually that a sequential approach – what you do 5 days, for instance, of azacitidine followed by 5 days of lenalidomide could have significant activity in high-risk MDS, but other studies actually suggested
that perhaps there is no effect, and I just saw some data that maybe a combination may be inferior.

I think actually this may be very dependent on the doses and the schedule of the lenalidomide that are used in the studies, but I'm not sure at this point whether this is going to be in a strategy that is going to be formally taking into some major trial.

So, the only combination right now that we're pushing in a significant way is the combinations with PD-1 and PD-L1 inhibitors with the hypomethylating agents. I think that is a story that is evolving around this concept that hopefully will be an attractive one. But I think the dynamics of response with these immune checkpoint inhibitors are going to be different from what we are accustomed to, and it may take some time, actually, to see a robust clinical benefit from this type of combination. So, we're going to have to learn how to use it.

There are other compounds that are being used with these hypomethylating agents, but the studies are way too early, and I will consider them almost as anecdotal – like hedgehog inhibitors. So, there are other approaches that are being put together in terms of potential doublets, if you will, but they are very early on for us to really know whether they will have any potential.

So, at this point we are most interested in this PD-1 inhibition with HMAs.

There are some other forms perhaps with mild cytotoxic forms of therapy, like there's some experience with vosaroxin and hypomethylating agents, but they are actually small trials and very early on for us to know.

In terms of mechanistic combination, I think the only one left at this point is this the PD-1/PD-L1 combination with azacitidine.

[SLIDE 70]

Dr. Steensma:

Great. Well, I'd like to thank my colleagues for sharing their insights in this program, “Tailored Therapies for Myelodysplastic Syndromes.” Please take a moment to take the posttest and complete the evaluation form in order to receive CME credit. Thank you for joining us.