OncologyEducation
a Think Research company

Optimizing Care for Patients with Myelodysplastic Syndrome (MDS)

[00:00:09.89] Hello, Heather and Brett. I'm very glad to introduce this OncologyEducation sponsored discussion about optimizing the care of patients with MDS, with a focus on novel oral agents for MDS, specifically oral decitabine in the care of MDS patients.

[00:00:35.69] I'm Rena Buckstein. I'm a hematologist at the Odette Cancer Centre, who has an interest in MDS research and run the National MDS registry called MDS can of which Brett and Heather are partners in crime in this registry.

[00:00:54.59] Joined with me is then Heather Leitch from St. Paul's Hospital, who is a clinical professor at the University of British Columbia with significant expertise in the care of MDS patients, and whose research interest is particularly focused or involved in iron overload. And she's a world expert in iron overload in MDS.

[00:01:18.97] And we're also joined by Brett Houston, a hematologist at the Cancer Care Manitoba, who has taken huge leadership in clinical trials in MDS and leading some national clinical trials in MDS, and also has an expertise in this and myeloid cancers.

[00:01:41.37] So I thought I would lead off this discussion with some questions that I hope you will both address in your presentations. We're going to be discussing some key evidence presented at ASH and at EHA in the last year that addressed these questions, and at the very end, we can have a little bit of a dialogue about some of the nuances.

[00:02:04.45] So my questions to you are when you're in the clinic, how do you decide when to use azacitidine versus decitabine in the care of your MDS patients? What do you consider? Is there any evidence that AZA or decitabine is better than the other with regards to response rates or durability of response or survival? Are there specific subsets that benefit more from one versus the other? What goes into your thinking about using them?

[00:02:34.48] And specifically, in patients with TP53 mutations, does that sway which hypomethylating agent you consider? Do you ever use combination therapy? And finally, with regards to combination therapy, is there a role for the addition of venetoclax to hypomethylating agents in MDS? And so I will hand over the presentation to Heather, followed by Brett, and then we will briefly discuss some of these abstracts at the very end.

[00:03:10.48] Thanks, Rena. So I'm going to be talking about the incidence of TP53 mutations and treatment strategies. This first abstract, and the real-world preference data on the use of parenteral versus oral HMAs. And then Brett will be talking about use of HMAs in combination with venetoclax in higher-risk MDS, and two abstracts addressing

that, including-- sorry, one specifically addressing oral decitabine with venetoclax in MDS.

[00:03:46.66] So I wanted to start with a case. And I'm just going to see if I can move some of this because I can't see my slide. Thank you. So this is a patient that I saw in 2024. She was age aged 64, and I inherited her from a colleague. And I'm not able to advance. And she had a history of POEMS treated by a colleague with radiation therapy, and also required an autologous stem cell transplant with melphalan conditioning in 2016.

[00:04:18.17] So she presented to me with fatigue, which was progressive. Her hemoglobin was 63. She was transfused. We did a bone marrow that showed MDS. She had complex cytogenetic changes, and her myeloid panel showed a multi-hit TP53 mutation. So this is obviously a very serious diagnosis.

[00:04:38.75] Her IPSS-M was very high risk, which gives a median survival of one year and 28% progression to AML by one year. So we started her on full-dose DEC/C in April 2024, based on preliminary data that I'd seen at the most recent MDS foundation meeting two years ago, and which has since been presented in abstract form.

[00:05:07.53] She did have an episode of febrile neutropenia. After four cycles, she did become red cell transfusion independent, and her bone marrow biopsy, to my amazement, showed a complete cytogenetic response.

[00:05:21.62] So that leads me to the first abstract, which is oral decitabine cedazuridine in patients with MDS and TP53 mutations, a propensity score matched analysis from phase II and phase III trials. So DEC/C has been suggested to have activity in TP53-mutated MDS, as I just showed you.

[00:05:42.93] They looked at three groups-- wild-type, single-hit TP53 mutation, and multi-hit TP53 mutation. They found the complete response rates were similar, but the multi-hit patients received fewer treatment courses due to progression, and I've included the results that were statistically significant.

[00:06:02.68] Their median overall survival was 11.5 months for multi-hit, versus 22 for single-hit and 32 for wild-type. And they found their median follow up was 21.5 months and did a landmark analysis at four months, and found that stem cell transplant did not result in improved survival, and that will become important.

[00:06:29.68] So they did this propensity score and matched 47 patients treated with DEC/C and TP53 mutation to 47 with TP53 mutation treated with single-agent IV hypomethylating agents, and matched for age, ECOG, IPSS-R scores, and variant allele frequency. The median overall survival was 13.1 months for DEC/C versus eight months for those receiving parenteral HMA.

[00:07:00.18] So they concluded, in patients with MDS harbouring TP53 mutation, that DEC/C may improve outcomes compared to conventional single-agent IV HMA. And I should add verbally that allo transplant does not seem to improve outcomes.

[00:07:15.61] So getting back to our patient, by October 2024, she's still well. She's been transfusion independent for several weeks, enjoying a good quality of life. She actually decided against allo transplant as a quality of life issue before this abstract went online

just a few weeks later.

[00:07:35.22] Her DEC/C was initially dose reduced and then the cycles were-- this is after she achieved this cytogenetic response, and then I extended her cycles to six or seven weeks for bone marrow biopsy demonstrated myelosuppression. She was requiring the occasional transfusion by December, and she was admitted to hospital in February 2025 after cycle 9 with fever.

[00:08:00.20] Bone marrow showed progression to erythroid type of acute myeloid leukemia, and she died on the palliative care unit in early March 2025. So this patient got about a year out of DEC/C, which I was pretty impressed with, but it's a very sad case because she's still relatively young.

[00:08:25.72] So I'm going to move on to real-world use patterns and clinical outcomes for MDS patients initiating oral DEC/C or intravenous or subcutaneous hypomethylating agents. So they looked at-- this is by Amer Zeidan and his co-workers.

[00:08:42.94] They examined real-world treatment outcomes in MDS with DEC/C compared with IV or sub-Q HMAs using an electronic health records database, looked at 2,100 MDS patients, receiving HMA as a first line treatment, 405 of them received DEC/C and the remainder received either AZA or IV decitabine, with 1,200 receiving AZA and just under 500 receiving decitabine.

[00:09:12.58] They did report and show that the baseline characteristics were comparable between the DEC/C and parenteral groups. And they found a median AML free survival of 13.7 months in the DEC/C group versus 16.5 and 13.3 for the parental agents, with a very significant p-value.

[00:09:35.99] DEC/C had a 16% lower risk of AML transformation or death, again, significant. And the median real-world time to next treatment was 7.8 months, 9.4 for DEC/C, 7.4 for IV and sub-Q HMAs, and that was also significant.

[00:09:55.10] They found that DEC/C was 18% less likely to receive a next treatment with very significant p-value versus the parental agents in the adjusted model. And they concluded that DEC/C patients had significantly longer AML-free survival and real-world time to next treatment. So this supports consideration of DEC/C as an alternative to parenteral HMA.

[00:10:20.60] And so one of the things that my coworkers are working on is a MyeloCan study of starting DEC/C with three days versus five. As we all know, there are frequent dose reductions and dose delays required with five days of DEC/C, and seeing which patients benefit from this strategy.

[00:10:45.92] At our centre, we have a recently established myeloid clinic. And I think that because of the dose reductions and dose delays, I would consider referring these patients to that clinic where they have more of an infrastructure for dealing with glitches in the timing of therapy. And with that, I'd like to hand it over to Brett.

[00:11:14.96] Perfect. Thanks, Heather. So I have two abstracts that I wanted to talk about briefly. This is the first one, which is looking at oral decitabine cedazuridine or INQOVI,

combined with venetoclax versus INQOVI in high risk MDS patients. And this is a propensity score matched analysis.

[00:11:35.67] So in this analysis, they included III clinical trials, which evaluated oral decitabine plus or minus venetoclax among patients who had higher-risk MDS or CMML. In terms of methodology, they use logistic regression analysis with nearest neighbour matching. It all looked very reasonable, and they matched based on clinically relevant variables.

[00:11:59.52] And they showed that after their matching, the groups mostly looked the same, with the exception for differences in terms of IPSS distribution and marrow blast. I comment on that primarily because a propensity score analysis is really only as good as the matching is done. But importantly, they did show similar distribution of cytogenetic and molecular abnormalities, which is impressive.

[00:12:25.83] In this study, the time to best response was longer with single-agent DEC/C compared to combination treatment with DEC/C and venetoclax, which is similar to what we see in combination treatment with AML as well.

[00:12:41.85] The overall response rates using the 2006 IWG criteria were also higher in combination treatment at 90% compared to 64%, and the median overall survival was slightly better in combination treatment compared to oral treatment at 24 months compared to 19 months.

[00:13:02.08] I think one of the big take-homes, at least from the author group on this study, is that more patients who underwent combination treatment were able to proceed to transplant, which is an interesting concept, and maybe we can talk a little bit about that later. And that eight-week mortality was slightly increased in the combination group at 6% compared to 2%, with notable increases in terms of cytopenias, which is, I think, perhaps what we would expect with more neutropenia and thrombocytopenia. Although, at least in this cohort study, no increase in major infectious complications.

[00:13:44.47] In terms of the second abstract, so again, sticking with the combination therapy theme here. This is an early-phase study that was looking at DEC/C and venetoclax in patients with, again, higher-risk MDS or CMML. This was a dose escalation expansion study and really reported on preliminary results because this study is still enroling.

[00:14:12.02] So they did restrict a patients with elevated blasts. So the blast count needed to be greater than 5%. And in terms of dosing strategies used, most of the patients received DEC/C for days 1 to 5, which is pretty typical, combined with venetoclax on day 1 to day 14, which is consistent with the VERONA trial that's waiting to be reported.

[00:14:40.15] And in this study, they included 39 patients overall, 9 in the phase I trial and 30 the phase II. They didn't find that the maximum tolerated dose was reached in the phase I, so they proceeded with the dose that I had mentioned previously.

[00:14:54.79] They found in terms of safety, that most of the common adverse events were related to hematologic toxicity, which is not surprising with grade 3 or 4 thrombocytopenia, and 85% of patients in grade 3 to 4 neutropenia and 74% of patients,

actually thought that number would be higher, and a febrile neutropenia rate of 21%, which, again, is even maybe a little bit lower than I might have expected.

[00:15:19.73] Median follow-up time was not long. It was just under 11 months, with a very impressive overall response rate of 95%. And in this cohort of patients, a very high percentage of them did proceed to an allo transplant at just under 50%, which is very impressive. But it's also clinical trial patients at MD Anderson, so we always have to take that into consideration as well.

[00:15:47.12] And so in terms of my conclusions and future directions, so I think that combination therapy, which HMA and venetoclax could be promising in both MDS and CMML.

[00:16:01.10] And these are very early studies. And in terms of early-phase studies, we've commonly seen very impressive results in high-risk MDS that haven't translated in the phase III. So I think that the VERONA trial will be very important in terms of looking at combination HMA and venetoclax in high-risk MDS. But in terms of preliminary data, we did see an increased overall response rate and an increased proportion of patients who are able to receive a transplant.

[00:16:34.76] And it always seems like it's coming soon, but I think it's actually coming soon. And so the phase III VENORA will be very informative in terms of how we can implement combination therapy in high-risk MDS. And I'm very excited because patients want oral therapy. I guess that was all I was going to say. Although, as we'll talk about, I think toxicity mitigation will be very important in this patient population.

[00:17:04.26] So thank you both for reviewing those abstracts. I'm going to ask you each some pointed questions relevant to your abstracts. So first of all, Heather, with regards to the abstract about monoallelic versus biallelic TP53 mutations, the dogma, at least from analysis from the [? IMRA ?] database, was that the outcome for monoallelic mutated disease was similar to wild type for MDS patients.

[00:17:34.81] But yet your survivals for monoallelic are inferior to wild type using decitabine. What are your thoughts about that? And when you're treating patients with monoallelic TP53, do you still consider them higher risk?

[00:17:52.74] Yeah, I think that's a really good point. So I think we have to keep in mind that this trial was not strictly controlled. It was comparing apples and oranges as well as they could with their matching and so on.

[00:18:12.16] So I think one thing we can all agree on is multi-hit TP53 is very bad. And for that reason, I said to this patient, we know you're going to need dose reductions. We know you're going to have dose delays, but we're going in full dose, and we'll just deal with the consequences. And one of the things I find really interesting about the combinations with venetoclax is whether that actually improves outcomes in multi-hit TP53 mutated MDS.

[00:18:43.18] But coming back to your question, yeah, I think that I would be maybe a little bit less excited about monoallelic TP53 mutation and more willing to accept that they might behave more like the usual higher-risk MDS, with the caveat that they might acquire a second mutation on the way. And I wonder if they might be more likely to do

that than someone without a TP53 mutation at all. You would think they would.

[00:19:15.56] Yeah, I agree with you, but certainly I think the [INAUDIBLE] of the monoallelic TP53 has some prognostic importance. We know that with deletion 5q that the variant allele frequency for monoallelic can upstage somebody with del(5q) to a prognosis that's intermediate between wild type and biallelic. So it may be playing a role because not all groups have replicated that [? IMRA ?] data, suggesting that monoallelic is just as good as wild type.

[00:19:50.05] And when you have a patient in front of you and you have to decide who has higher-risk disease, let's take out TP53 mutated disease. Let's say wild type but higher-risk disease, what goes into your decision-making in choosing hypomethylat-- which hypomethylating agent do you choose for your patient? Do you talk to them and give them the options? I think most patients would prefer oral over parenteral, but what factors into your decision-making in choosing one over the other? And that's open to both of you.

[00:20:30.50] I can start there. I'm not actually sure if my practise is the same as yours, Heather, but I think I do offer both. I will say that I haven't started an MDS patient on azacitidine in probably more than 18 months. So that might reflect partially my counselling also, which you'll hear.

[00:20:52.52] But I think it's important to acknowledge that there is no head-to-head trials comparing azacitidine and decitabine. And that azacitidine does have RCT-level evidence for an overall survival benefit, whereas decitabine does not. And that there is a tonne of meta analyzes and network meta analyzes and propensity matched cohort studies that aim to compare these two, but I think that our level of certainty in terms of the relevant effectiveness of both of these is low.

[00:21:25.66] So I offer people the option for both. I say that azacitidine might be better. It has a stronger evidence of survival compared to decitabine. But at the end of the day, oral decitabine is far more convenient. And I think the benefit of both of these therapies is unfortunately modest.

[00:21:47.43] And we're really comparing like months' differences between the two. And when you tell people that their anticipated survival is one to two years, in my experience at least, most of them haven't wanted to come to clinic for subcutaneous injections for a week out of a month, kind of thing.

[00:22:05.61] I will say that I find oral decitabine quite toxic, and so I do start, like, with five-day dosing in patients who are younger and who don't appear to have a lot of frailty. But I will say that in patients where I'm a bit worried, or certainly in patients over the age of 80, I typically start at three days. And 80 is a bit arbitrary, but as I've used this more, I've dose reduced more as well.

[00:22:41.79] Yeah, I have to say that, I don't know if my practise is different from yours, but I seem to see a lot of 80-year-olds and 85-year-olds, so I do have more of a comfort level with the use of azacitidine. And part of that comfort is that the nurses in our medical short-stay unit who are administering the medication can help keep an eye on them, particularly in the early days.

[00:23:06.69] So I have to say that until recently, azacitidine has really been my go-to treatment. However, I agree with both of you that for a younger patient, like this patient that I presented, I would be a lot more open to offering an oral option, with the caveat that they have to understand that there will be dose reductions and dose delays, and that may affect their plans. Lots of my patients have travel plans, for example, want to fit it in between cycles of whatever it is they're receiving.

[00:23:45.00] The other patients that I would really lean toward oral decitabine are those that live at a distance from a treatment centre, so that it's just not practical for them to come in for seven days out of 28, although they do still have to come in for transfusions, for example.

[00:24:04.33] But I am moving more towards the oral option as we gain more experience with it. But I've maybe been a bit slower than you have, Brett, for example. Although now, as I mentioned, that we do have that myeloid clinic with infrastructure, it may be easier to monitor these patients and keep them safe.

[00:24:28.93] Thank you. The one thing I wanted to mention, Brett-- no, Heather, actually, about the abstract you presented, the real world evidence from Amer Zeidan using a large health database where they matched patients. Reading the fine lines of that abstract, they talk about the fact that 20% were higher risk in both.

[00:24:54.38] But they don't actually state how high risk was defined, and I suspect it was based on excess blasts because those billing administrative databases don't often have risk scores. So it's extrapolation to real-world patients that we see may not be completely doable because most of us are using HMAs in higher-risk disease.

[00:25:24.96] And many of the provinces only fund it for higher-risk disease, intermediate or high-risk disease. And so in that population, they had more lower-risk disease because only 20% were higher risk, just to point out there, and that the matching between the two populations may not have been perfect.

[00:25:42.65] And then just in the last few minutes, are you using venetoclax right now off label in combination with HMA in any of your MDS patients? And if so, who are you offering it to? And are you dose-reducing your chemotherapy or your venetoclax in any way?

[00:26:03.98] Yeah, maybe I'll start with that one. So the vast majority of my patients don't have access to venetoclax. They can't afford it. And unless they've got a good government job that they're retired from, they don't have third party coverage.

[00:26:20.16] I do have one patient with higher-risk MDS who, impressively, is on cycle 79 of azacitidine. So he's doing very well, although he feels like a pincushion for sure. But he does have coverage. And so we've discussed for a long time that when he does progress, that we will give him DEC/C plus venetoclax if we can get his private insurance to cover it.

[00:26:45.35] Just to address a couple of your points, Rena. So first of all, I have not used DEC/C in IPSS intermediate one patients. I mean, we don't really calculate that score a lot anymore, but I think that many of them are going to actually be higher risk in the IPSS-R

and IPSS-M. So I do think of it as a treatment for higher risk.

[00:27:10.71] Yeah, and in terms of adding venetoclax, I mean, one type of patient that's really we have very limited options for is those with multi-hit TP53 mutation. And I think the future of these analyzes is going to be, OK, which molecular subtypes benefit more and less, not just TP53 but other mutations as well, or mutations without TP53.

[00:27:40.08] [INAUDIBLE] excel one.

[00:27:41.88] Yes.

[00:27:42.54] Brett, do you want to talk about the use of venetoclax in combination with HMA? Just to the final word.

[00:27:47.59] Yeah, yeah. I do not routinely reach for that yet because I don't think that we have convincing evidence that it is better and safe. A couple of times I have used combination. I've actually used azacitidine compared with venetoclax, primarily because that's where our local experience has been with AML therapies in very young MDS patients as a bridge to transplant.

[00:28:15.34] So we give a couple cycles of combination HMA-VEN, and then we go directly to transplant. And I mean, those numbers are very small. It's worked both times. But I think that might be something that warrants further exploration in the future for sure.

[00:28:33.87] Well, thank you very much for your time on this Friday afternoon. And I think thank you to our listeners. And I think we'll stop here. Please feel free to contact us with any of your MDS-related questions.