Hypomethylating Agents

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Welcome to *Managing MDS*. My name is Dr. Guillermo Garcia-Manero. I am a Professor of Medicine in the Department of Leukemia at the University of Texas MD Anderson Cancer Center and the Head of the Section of Myelodysplastic Syndromes and Deputy Chair of Translational Research. I am live at the 58th American Society of Hematology Annual Meeting. Today, I will be reviewing four abstracts presented on hypomethylating agents in myelodysplastic syndromes.

So, the first study that we are going to discuss is the Phase 2 study of guadecitabine, also known as SGI-110, in high-risk MDS patients who are refractory or relapsed after azacitidine. So, the first question is, how does guadecitabine, or GDAC, work? So, this is a very interesting molecule. It is a second-generation decitabine-like compound that is basically a dual molecule as compared to decitabine, and by having this structure, it is a more powerful inhibitor of DNA methyltransferase. So, the expectation is that this drug actually would be a more potent hypomethylating agent. What is interesting, because we have studied this drug in multiple studies actually, is that despite the fact that it appears at least to be more potent, the compound actually does not have clinically more toxicity. So, the study that the French group presented today is very interesting and actually serves as the basis for a Phase 3 trial that is ready to start worldwide for this indication, and the concept is very important. Most patients that receive a hypomethylating agent like azacitidine or decitabine eventually will lose response to the first-line therapy. We call that hypomethylating agent failure disease, and the problem is that most of these patients become resistant or refractory to other types of therapies, and the prognosis actually is quite poor with a median survival of around 4 to 6 months. We are desperate for second-line type of approaches, and the question is why will a drug like SGI-110 or guadecitabine have activity in this context? At the ASH meeting a couple of years ago, I presented data from a study that was conducted in North America where we showed that this compound had activity in this group of patients with HMA failure disease, probably because this is a more potent inhibitor of DNA hypomethylation. In this trial, these French investigators, with Dr. Fennaux, used the standard schedule, that is, 60 mg/m^2 daily for 5 days. What they have shown is that the compound as we know in the front-line setting both in MDS and AML is actually very well-tolerated. Of course, it has hematological toxicity, but this is kind of expected. The key numbers that the French group showed was an overall response rate of around 60%, a median duration of response of 9 months, and a median overall survival of around 7 months. These numbers are positive, but I have to say that they are a little bit at the borderline of what I will consider as likely to be an improvement, compared to other approaches in HMA failure. That said, this is a smaller study that is probably not enough for the question that we have. The bottom line is that I think this data supports the use of this compound on the Phase 3 study that we are ready to launch, and we hope that this is a successful intervention that will help our patients with HMA failure. This is a major need for our patients.

This was actually anteceded by a presentation by one of my fellows Dr. Guillermo Montalbán Bravo, where we actually presented a study, a Phase 2 trial of the same compound, guadecitabine, but in this case in patients with previously untreated disease. The data that we presented here was on 50 patients with higher-risk disease, meaning intermediate-2 or high risk by MDS IPSS criteria. They dosed the same as on the prior study, 60 mg/m^2 for 5 days, and then basically, we wanted to have an idea of the response safety and potential for overall survival, event-free survival. As we have seen with the other hypomethylating agents, this drug is actually very well-tolerated. I have to mention that this is a subcutaneous drug, and we actually have minimal skin toxicity. Overall, I think that the toxicity profile is very positive. Now, there were some reductions needed for cytopenias, but I think the key data here was that we showed what I think is a very interesting response rate with an overall response rate of 61%, complete remission rate of 23%, and, importantly, a complete cytogenetic response rate a little bit over 20%. These numbers actually compare very well with the original data with decitabine where, depending on the study you look at, the complete remission rate for instance was below 10%. The median survival was around 15 months, and the median event-free survival was 10 months. Now, when this paper was presented at the meeting, a couple of the members of the audience asked this question: in terms of the survival, it does not look to be better than, for instance, what we saw on the original azacitidine randomized trials. I think the answer is that the characteristics of these patients on this trial are very poor with a very high rate of cytogenetic alterations and some p53 mutations, and also, I think that all of us acknowledge that a 24-month survival on the original AZA-001 trial actually was too long. I think that this data for sure supports the use of SGI-110 or guadecitabine in the front line. This compound actually has been studied on a major AML trial. We probably are going to have to wait for the results of this AML trial before we move on the front-line setting in MDS, and of course, I mentioned earlier the Phase 3 trial of HMA failure disease. We are actually very excited about this compound, not only because of its activity but also because of its toxicity profile.

The next presentation is a study that was presented by Dr. Jabbour, also from my group, where he presented data from one of the first randomized Phase 2 studies of low-dose hypomethylating agent; in this case, decitabine versus azacitidine, but in patients with lower-risk disease. I think this is a very important study. For years, we have been using the doses of decitabine and azacitidine that are standard for high-risk disease, but in patients with lower-risk disease. Of course, this has toxicities and so forth. I led a study with oral azacitidine that showed the PK profile of oral azacitidine, that is a very active drug, actually was very low. This for me suggested that perhaps we could come with lower doses of decitabine or azacitidine. We have modeled this mainly with decitabine in a number of papers including one a couple of years ago in the *Journal of Clinical Oncology* (JCO). So here, we wanted to get more experience and perform a variation randomized Phase 2 trial of two schedules of decitabine and azacitidine where we give the drug for each compound on a 3-day basis: so azacitidine 75 mg/m^2 for 3 days once a month or decitabine 20 mg/m^2 for 3 days once a month. What we see on this type of approach, first of all, is that these are extremely well-tolerated as opposed to what you see with the other compounds, and we see a very striking response rate, particularly with decitabine. Indeed actually in this trial the low-dose decitabine arm was superior to the low-dose azacitidine trial. Now, the question is why is that the case? And I think basically what is happening here is that perhaps we are not using "an equimolar" azacitidine schedule compared to what we do with decitabine. So, probably one should compare 3 days of decitabine with maybe 5 days of azacitidine. We are already doing this in a consortium trial that I am leading where we are comparing 5 days of azacitidine and 3 days of decitabine, 3 days of azacitidine versus randomization to observation in transfusion-independent patients. The message from this study is that this is extremely active in low-risk

disease with an excellent toxicity profile. We just need to figure out whether we use low-dose decitabine or low-dose azacitidine, and I think the studies are going to pave the way for the oral hypomethylating agents that hopefully will come soon.

So, let me summarize actually what I mean by effectiveness. The overall response rate in these patients with lower-risk disease was over 50% with a CR rate (and I am reemphasizing this complete remission rate) with azacitidine of 38% versus 30% with decitabine. We saw responses, cytogenetic-wise, that were complete in almost a quarter of the patients treated with decitabine, and a third of the patients treated with decitabine actually became transfusion independent. Also, what was very important is that we have not reached a median survival rate, so that is not reached actually in a group of patients with full characteristics, and the median event-free survival was 13 months for azacitidine versus 19 months for decitabine. How could these data impact my clinical practice? I think this is very important and it is actually starting to become standard of care where these patients with low intermediate-1 disease myelodysplastic syndrome probably should be treated with this attenuated dose schedule of either decitabine or azacitidine, because you have less toxicity, and I think at the end even more activity than what you see with the standard type of approach. Again, I think at some point in the next few years, we will have either an oral azacitidine compound or oral decitabine that will probably give us PK profiles similar to what we are trying to do here. I think these data are going to be very important for our daily clinical practice.

To finish, we are going to review a presentation by the Italian Group on an Italian Registry of Clinical Outcomes with patients with MDS treated with azacitidine. These are patients that are treated I guess outside the context of a clinical trial in Italy. I think this is an important study because most of the data that we have are from this AZA-001 trial that is probably one of the best conducted randomized clinical trials ever. The data is very good, the response is very high, survival is very high, and the question is whether this data is true or not. Many of the other registry studies actually have shown inferior results to this AZA-001 trial, but actually in this study, we see very positive data also with azacitidine in this particular context in Italy. They looked at almost 1,800 patients with myelodysplastic syndrome seen in Italy from 2009 to 2014, and they identified 420 patients that had received azacitidine. The overall survival at 1 year was 73%, median survival of 23 months (that is basically identical to what the AZA-001 trial showed), and importantly, they also were able to compute outcomes after azacitidine failure with a survival of around 8 months. They had a very impressive complete clinical response of around 69%, a CR rate of 12% that actually interestingly is lower than what we saw on AZA-001 trial, and a PR rate of around 20%. Median number of cycles for response was 6 (that is basically what was shown in the original study) and as we know happens after median of 16 months, 77% or so of the patients had discontinued therapy, with an evolution to AML or progression of around 32%. What this data is indicating is that now, several years after those randomized trials, and I see that in my practice, community physicians are really masters at using these compounds, both azacitidine and decitabine. We are starting to see how the proper use of this kind of compound is associated with what I think are excellent clinical results in the context of giving, kind of like, therapy outside a clinical trial. I think this is very important and it also helps us in the design of future clinical trials in terms of expectations.

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