TGF-β Inhibitors, Anti-TLR-2 Antibodies, and Deaminase Inhibitors

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Welcome to *Managing Myelodysplastic Syndromes.* My name is Dr. David Steensma. I am an Associate Professor of Medicine at Harvard Medical School and a faculty member in the Adult Leukemia Program in the Division of Hematologic Malignancies at Dana-Farber Cancer Institute in Boston. I am live at the 58th American Society of Hematology (ASH) Annual Meeting. Today, I will be reviewing four abstracts which were presented on novel therapies being investigated in myelodysplastic syndromes. The first is the study of OPN-305, a Toll-like receptor 2 antibody in patients with lower-risk MDS who had previously received a hypomethylating agent. The Toll-like receptor family is part of the innate immune system. Previous preclinical work has shown overexpression of Toll-like receptors 2, 4, and 5, potentially contributing to the marrow failure of myelodysplastic syndromes. OPN-305 is a humanized antagonistic IgG4 kappa monoclonal antibody against Toll-like receptor 2. The study was presented by Dr. Guillermo Garcia-Manero and was in patients who, at the time they were assessed and screened, fit lower-risk IPSS criteria, although they may have been higher-risk earlier so not a purely low-risk population, and they had previously been failed by hypomethylating agent. The patients with del 5q had already received lenalidomide. The patients were treated with the antibody at an initial dose of 5 mg/kg every 4 weeks for 9 cycles but then were escalated to 10 mg/kg after early pharmacokinetic information. All of the adverse events with this agent were grade 1, mostly minor GI toxicity. There was no significant drug-related toxicity and no excess infectious complications. This antibody is used in patients who have undergone renal transplants and so there is already an extensive safety database in that population, but this was the first time it was used in a hematologic malignancy. 17% of the patients became transfusion independent and some more patients did have minor hematologic improvements. So, this is an agent that is active and that is going to be studied further in patients who have not previously had hypomethylating agents, and potentially as combination therapy.

The second and third abstracts to discuss both deal with an agent called luspatercept. Luspatercept is an activin receptor ligand trap. It works by binding to members of the TGF-beta super-family, such as GDF11, which inhibits late-stage erythropoiesis. In healthy human volunteers and in various anemic populations, it increases hemoglobin levels and so it is being studied now in myelodysplastic syndromes. We have previously seen early-phase data from luspatercept presented at the ASH annual meeting in patients with lower-risk MDS. The abstract being presented this year by Dr. Uwe Platzbecker, examined 32 patients and described extension study with treatment up to 2 years. The grade 3 adverse events that were seen with luspatercept included myalgias, and some patients had a blast count increase although the relationship of that to the study drug versus just normal disease progression with time is unclear. Patients also experienced lower grade fatigue, bone pain, GI upset, myalgias, headaches, and some redness at the injection site. A substantial proportion of patients achieved transfusion independence or hematologic improvement. In patients who had low transfusion burden, 85% of patients experienced hematologic improvement, and in those with higher transfusion burden it was 79%. Most of the

patients who have responded to this antibody have either ring sideroblasts, *SF3B1* mutations or both. The reason for this genotype-specific activity of the drug correlation is unclear. The range of transfusion independence in some of the patients now stretches out to more than a year.

A companion abstract was presented describing pharmacokinetics and pharmacodynamic data with luspatercept. This examined the half-life of the drug and found that body weight correlated with luspatercept clearance such that heavier patients may need a higher dose. The investigators proposed a dosing algorithm for dose escalation in larger patients and in patients who are not responding to treatment.

The final abstract to discuss is a Phase 1 study of ASTX727 which is a combination of oral decitabine and an oral cytidine deaminase inhibitor in patients with myelodysplastic syndromes. Hypomethylating agents, azacitidine and decitabine, are the mainstay of therapy for higher-risk MDS, but they require frequent visits to the physician's office or to the infusion clinic because they are parenteral therapies. In addition, there are in vitro data suggesting that perhaps longer exposure to lower doses may be beneficial with hypomethylating agents, but you really cannot do that with a parenteral agent. ASTX727 is an oral form of decitabine which is combined with the cytidine deaminase inhibitor to prevent degradation in the gut and in the liver by first pass metabolism. This study demonstrated that pharmacokinetics virtually identical to that seen with injectable decitabine are achievable with ASTX727. In addition, pharmacodynamic data measured by LINE demethylation were also similar to parenteral hypomethylating agents. Therefore, this agent is now moving forward in a randomized fashion. The adverse effects that were seen were similar to what we would expect with hypomethylating agents including: cytopenias, GI upset, and other mostly minor problems, but some severe infections in neutropenic patients were seen. So, this agent is moving forward. There is also CC-486 which is an oral azacitidine which is also moving forward in the treatment of patients with myelodysplastic syndromes.

In 2016, we still only have three drugs that are FDA-approved for myelodysplastic syndromes, azacitidine and decitabine, which are primarily used in higher-risk patients, and lenalidomide, the label for which includes del 5q lower-risk patients, but which also sees extensive off-label use in non-del 5q patients. There are a number of areas of unmet needs in myelodysplastic syndromes. Most acute among them are patients with lower-risk MDS who are failed by hematopoietic growth factors and/or lenalidomide and/or low-dose hypomethylating agents, and patients with higher-risk MDS for whom hypomethylating agents either are not tolerated or fail. These are areas in which a number of novel therapies are moving forward. In the higher-risk patients, we are seeing the advent of combination therapies. A number of drugs are being combined with hypomethylating agents in ongoing clinical trials that were not presented here at the meeting because the data are not yet mature. These include drugs like venetoclax (ABT-199), vadastuximab (SGN-CD33A), and others. Rigosertib is a polo-like kinase inhibitor which is being studied in patients for whom hypomethylating agents have failed as a monotherapy, in a randomized fashion. In the lower-risk patients, there is a lot of interest in development of splicing inhibitors such as H3B 8800. Across the MDS spectrum, we are struggling with how to incorporate checkpoint inhibitors and other immune-modulating therapies into treatment. A number of combination studies across the disease spectrum with checkpoint inhibitors plus hypomethylating agents are ongoing. We do not have any data yet from those trials, but given the efficacy of these agents in solid tumors, there is considerable interest in using them in myelodysplastic syndromes. Thank you for viewing this activity. For additional resources, please be sure to view other educational activities on *ManagingMDS.com*.