Pracinostat with Azacitidine in the Treatment of Patients with MDS

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Hello, everyone. This is Ehab Atallah. I work at the Medical College of Wisconsin. I specialize in leukemia and MDS. Today, we will be discussing our poster presented at ASCO on the role of pracinostat with azacitidine in the treatment of patients with MDS. Just a little background overall for histone deacetylase inhibitors which is what pracinostat is, it's a histone deacetylase inhibitor that has really good pharmacokinetic and pharmacodynamic data compared to older histone deacetylase inhibitors.

As you all know, hypomethylating agents are the only FDA-approved treatment for the treatment of patients with high-risk MDS. The way that hypomethylating agents work is that they induce epigenetic changes which induce differentiation in the bone marrow, and the theory behind adding histone deacetylase inhibitors is that they work synergistically to induce this differentiation in the bone marrow. So, in the lab this combination of a histone deacetylase inhibitor and a hypomethylating agent has been very, very exciting and promising. However, there have been many studies using histone deacetylase inhibitor combination with hypomethylating agents that have not really panned out in the clinic to have a benefit. Pracinostat again has a really good PK and PD data and was evaluated in a randomized phase II study of azacitidine with pracinostat versus azacitidine alone. In that study, there was really no difference between both arms; however, looking back, a lot of patients who were on the pracinostat arm discontinued treatment due to side effects such as fatigue and diarrhea. When looking back at that study and looking at patients who stayed on treatment who may think that treatments with pracinostat, they actually did quite well. So then the question became did they do well because they stayed on the pracinostat or they were doing well and that's why they stayed on the pracinostat?? So, which one, the chicken or the egg sort of story here? So, this idea of if we keep patients on pracinostat, will they have a better outcome? And this phase II study was looking at the reduced dose of pracinostat, which is 45 mg three times a week for three weeks of each four-week cycle in combination with azacitidine, will that lead to better compliance? The randomized phase II study that I spoke of earlier, the dose of pracinostat was 60 mg three times a week for three weeks, every four-week cycle in combination with azacitidine. The initial part of the study before the study was expanded to 60 patients, the initial part was to see if we will be able to maintain patients on this 45 mg dose. And sure enough we were able to maintain patients on the 45 mg. The study was then expanded to 60 patients to evaluate efficacy Overall, 64 patients were enrolled and the median follow-up was 17 months. Overall it was well tolerated and the 31 patients remained on treatment and about 70% discontinued treatment, approximately 25% was because they proceeded to stem cell transplant and 17% due to disease progression, and only 11% stopped due to AEs. The most common AEs were constipation, nausea, and fatigue. In my clinic, fatigue has been significant with the 60 mg, however with the 45 mg patients tolerated it better. The interesting thing is that the overall response rate was 33% with all of those being complete remission. There was

also on top of that 34% of patients had a marrow CR. The encouraging data is that the one-year overall survival in these patients with high-risk MDS was about 77% and the median overall survival was 23 months. So summary of this is that this data is encouraging using a lower dose of pracinostat that patients are able to stay on it. It seems to have a pretty good complete remission rate when compared to azacitidine alone. Of course this is not a head-to-head comparison, and I think the next step is to move to another end of my phase II study using the lower dose of pracinostat and see if this benefit can be seen compared to azacitidine alone in patients with high-risk MDS.

Link: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.7556

Reference: Atallah EL, Khaled SK, Cooper BW, et al. Phase II study of lower-dose pracinostat plus azacitidine safety and efficacy in patients with high/very high-risk myelodysplastic syndromes. Abstract 7556. ASCO 2020.