Genomic biomarkers to predict response to hypomethylating agents in patients with MDS

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Welcome to Managing MDS, I am Dr. Aziz Nazha. I will be discussing one of the abstracts that we presented at the 2017 American Society of Hematology Annual Meeting in Atlanta on genomic biomarkers to predict response to hypomethylating agents in patients with myelodysplastic syndromes. Treatment with hypomethylating agents azacitidine and decitabine can improve outcomes in MDS. Identifying biomarkers that can predict response is clinically important because it can prevent prolonged exposure to ineffective therapy, avoid toxicity, and more importantly, save cost. There had been several studies that evaluated the impact of molecular data on response to hypomethylating agents, and some of the mutations such as TET2 or TP53 have been shown to predict response to this therapy. The challenge with these data is that a mutation that can predict response in general does not mean that the mutation can be a biomarker for response. For example, if you have IDH2 mutation and you add an IDH2 inhibitor, the IDH2 mutation is not a biomarker for response because approximately only 30% to 40% of the patients will respond to the therapy; 60% of them will not. We have thought about whether there is a way that we can incorporate genomic data and study the association between these genomic data to provide a tool that can be built with genomic biomarkers to predict response to hypomethylating agents. In order to do that, we used the recommender system algorithm. This algorithm has been used by Amazon, Netflix, and other companies to try to predict products for their customers. For example, if the customer watched this movie and this movie and this movie, can we predict the next movie that the customer will watch? We used that same analogy and we said that if the patient has this gene, and this gene, and this gene, can we predict if this patient is going to respond to therapy or not?

We compiled clinical and mutational data on a patient cohort of 433 patients treated at our institution and other several institutions in the United States from the MDS Clinical Research Consortium. We first evaluated the impact of every single gene on the response, and the only gene that had predicted resistance was NF1. We then combined a couple of mutations to try to see if that is what would predict response, and we could not build any reliable model to do that. Then when we applied the recommender system to our patient cohort, we were able to identify 8 association rules, or 8 rules of genes that are associated with each other that can predict resistance to hypomethylating agents, and one rule that can predict response. When we applied
these rules into a validation cohort, we were able to predict with 95% confidence that the patient will have resistance to hypomethylating agents in approximately 30% of the patients. The accuracy of that prediction was 85%. We believe that genomic biomarkers may predict response to hypomethylating agents, and I think it is important in this project that machine learning algorithms, especially the recommender systems and others, may open opportunities for us to take advantage of genomic data and translate this information into useful clinical tools.

Thank you for viewing this activity.

Reference: