The Future of Genomics in MDS: What Will We Require for Our Clinical Daily Practice?

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Hello, welcome to *Managing MDS*. I am Jaroslaw Maciejewski, and today, I will be providing highlights from the 14th International Symposium on MDS in Valencia, Spain. The topic of my presentation and the focus of my research interest is the genomics of MDS. Today's presentation will address the issues of future genomics in this disease. What will be required for our clinical daily practice in terms of molecular genetics and genomics in MDS?

The objectives of this presentation are to highlight the newest advances in genomics of MDS, to point out new developments and applications of genomics in MDS, and to summarize currently available molecularly targeted agents that rely on molecular markers derived from mutations discovered in myelodysplastic syndrome. With the introduction of next-generation sequencing and deep sequencing technologies, new discoveries were made in terms of the key pathogenic factors in myelodysplastic syndrome. These include somatic mutations and the recognition and appreciation of clonal heterogeneity and clonal architecture and its dynamics throughout the course of the disease. Initial ancestral hits initiating the pathophysiologic cascades are followed by subsequent hits making the clonal architecture very complex. Thus, the molecular heterogeneity is derived from the variety of mutations present and their combination, as well as the succession in which these mutations occur in individual patients. This heterogeneity on a molecular level explains the diversity of clinical courses of patients. This is a very important realization and it explains why patients with similar features might have disease progression along different trajectories. Thus, the discovery effort included identification of novel mutations present in myelodysplastic syndrome, the pattern of the occurrence, and combinations present in patients. The discovery phase of using next-generation sequencing in MDS is now followed by an application phase, and identification of suitable clinical applications for molecular diagnostics in the disease. Principally, there are several new applications. For one, mutational diagnostics might help us to secure the diagnosis and distinguish myelodysplastic syndrome from possible mimics. This is an important objective tool that pathologists will have in addition to cytogenetics to make a proper diagnosis of MDS.

The second application includes the distinction of individual MDS sub-entities; for instance, myeloproliferative syndrome, myeloproliferative MDS, overlap syndromes from MDS or from different stages, and variants of myelodysplastic syndromes from each

other, based on molecular profiling. Certain mutations or their combination might convey prognostic application. There are several new mutations that have been identified, and all the mutations that have been known for years that now provide important prognostic information to a physician, which might affect clinical management. In the meeting in Valencia, several examples of this type of application were given. For instance, discussion has focused on the presence of spliceosomal mutations and prognostic implications with regard to spliceosomal mutations (grouped or individual) and mutation in individual genes. In Valencia, similar to other meetings recently, the role of p53 mutation has been discussed with regard to prognostic implications for future treatment and management, including bone marrow transplant.

Finally, a great deal of emphasis has been given to targeted applications of molecular genomics. Clearly, certain mutations present in myelodysplastic syndrome constitute very good molecular targets. While current traditional therapies have been applied across the board to patients characterized based on their clinical features, more and more, the rational application of drugs will include consideration of molecular patterns present in individual patients. Thus, for example, traditional therapies such as hypomethylating agents and erythropoietic agents might be applied based on molecular profiling. Identification factors which might be known to preclude responsiveness or be specific sensitivity markers would increase the likelihood of a patient to respond to the given therapy. In particular, the identification of p53 mutation in some patients who have responded to hypomethylating agents was important, and thus the presence of p53 mutation in contrast to the traditional cytotoxic therapy might not preclude responsiveness to hypomethylating agents; an important finding. Finally, individual lesions (such as mutation in spliceosomal genes, growth factor receptor genes, and others) might be targeted by specific drugs.

One of the most important findings presented at the Valencia meeting was the fact that sotatercept, which is a new erythropoietic agent that improves anemia based on blockage of TGF pathway, is particularly effective in patients with SF3B1 mutation in whom the response rates are maximized. The nature of this interaction between the drug and mutation is unknown, but, similar to the case of 5q- in lenalidomide, there is a strong relationship with responsiveness and the presence of a particular molecular lesion. Spliceosomal mutations are, however, specifically targeted by the new class of agents called spliceosomal inhibitors, which utilize the principle of synthetic lethality. Most of the spliceosomal mutations are heterozygous. Thus, the cells that are affected by these mutations can handle inhibitors of splicing, the same way as diploid normal cells with wild-type spliceosomal genes, and therefore are specifically sensitive to spliceosomal inhibitors that are currently being developed. Another example known from the past is, of course, the development and current approval of FLT3 inhibitors in patients who carry FLT3 mutations. This would be mostly applicable to patients with acute myelogenous leukemia and FLT3, but some occasional patients with MDS might have FLT3 mutations IDH1 and IDH2. We have no specific inhibitors of IDH1 and IDH2 close to approval for clinical practice and thus molecular profiling and identification of

IDH1 or IDH2 mutations will prompt application of targeted therapies alone or in combination with hypomethylating agents. The number of targeted agents will increase steadily over the next couple of years, and thus, the molecular profiling will in my opinion gain more and more importance. It is important to note that molecular markers based on mutations might be helpful to monitor minimal residual disease and therapy efficacy based on the clonal burden concept, because deep sequencing allows for quantization of the number or the fraction of cells carrying particular mutations. Targeted agents are likely to decrease this fraction and predict the maximum therapy response on a molecular level, as well as propensity for relapse. The number of targeted agents will grow with multiple developments targeting individual genes such as EZH2, DNMT3, TET2, and many others.

Thank you very much for your attention, and we are certain that this field of genetics as applied to myelodysplastic syndrome will evolve in the next couple of years. We expect even new findings as soon as by the next ASH meeting.