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What is the most practical way to risk-stratify patients with MDS?

Welcome to *Managing MDS*, my name is Rami Komrokji and I am Professor of Oncologic Sciences and Clinical Director in the Malignant Hematology Department at the Moffitt Cancer Center in Tampa, Florida. I am frequently asked, “What is the most practical way to risk-stratify patients with MDS?” Obviously, risk-stratification or staging in MDS is a very crucial step because first, that is the prognostic information we provide for the patient and their caregivers, and it is a tool for us to risk-stratify therapy accordingly. We are trying to weigh the risks and benefit of the procedures that we can recommend for these patients; namely allogeneic stem cell transplant, where there is 30-40% chance of cure but 20% mortality from the procedure itself. We try to estimate the risk of the disease to justify such recommendations. The disease risk typically refers to the risk of transformation to AML and, unfortunately, mortality from complications from the disease itself. But risk assessment is more inclusive than that, so one would think of patient-related risk factors and disease-related risk factors.

There have been several risk models to account for that. In real life, it is obviously very difficult to calculate all those models. I would say currently that the Revised-IPSS is probably the most reasonable model. The IPSS used to be the gold standard model for many years. We would weigh factors or variables such as the blast percentage in the bone marrow or the cytogenetics detected on the bone marrow, and divide those into risk groups and the lines of cytopenias. This served as the gold standard for many years for risk-stratification, but it also had some shortcomings, such as accounting for the depth of the cytopenia. There is no doubt that the newer risk models, the Revised-IPSS, addresses those shortcomings, and the Revised-IPSS had been validated in several data sets to show that it adds to the prognostic value of the IPSS. There are other models like the MD Anderson Global Prognostic Scoring System (MDAPSS) that also could be used.

In real life, obviously one would pick one clinical risk model and use that, and it seems like the Revised-IPSS is the most commonly used model. Patients are classified into five risk groups. This is based on, again, blast percentage, with more details than the classical IPSS. Concerning the cytogenetic information, again, there are much more detailed subgroups defining the good and the bad risk cytogenetics, and finally accounting for the depth of the cytopenia. Patients are divided into five groups from very low to a very high risk group. When we looked at risk models in lower-risk MDS, again,

most of the newer risk models would redefine or upstage around 15-20% of the patients that we would think are labeled as lower risk by the IPSS, but in reality, their disease has worse features. However, none of the models detect that completely in all the patients. If we look at patients that had, unfortunately, less than two years median overall survival, the newer risk models such as the Revised-IPSS can identify only half of those patients. Therefore, we start with the Revised-IPSS or a clinical model, but nowadays we complement those with some molecular data.

We have known over the past several years the prognostic value of somatic mutations added to the clinical variables. Nowadays, it is a routine test to check for somatic mutations using next-generation sequencing, and there are certain mutations that could add value to the clinical models. There is the seminal paper by Dr. Bejar that was published in the *New England Journal of Medicine*[1] showing that the presence of one of five gene mutations would upstage patients by one stage in their risk model, those have been looked at in the context of the IPSS-Revised. There are certain gene mutations that, if they are present, patients will be upstaged. Probably the most important to highlight is the p53 mutation, which is always regarded as a bad mutation in the setting of MDS, where patients are upstaged based on its presence. The other mutation, the SF3B1 mutation, is probably the only mutation that is associated with good risk. In addition to the mutation itself, we know that the number of mutations matters. Patients who have three or more mutations do not do as well, regardless of what those mutations are. Nowadays, when we risk-stratify those patients, we start with a clinical risk model, such as the Revised-IPSS, we look at the somatic mutations in terms of number and whether there is any one of those high-risk mutations, and that will allow us to know the disease risk in general. Then we weigh in on the host-related factors, so we look at the comorbidities of the patients, the functionality – because obviously, there are patients who are frail without significant comorbidities and the other way around – and we put all those factors together and we come to a disease and host risk assessment in a way. The next step is discussing that with the patient and tailoring the therapy according to that risk assessment.

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Reference:

[1]Bejar R, Stevenson, Abdel-Wahab O, et al. Clinical Effect of Point Mutations in Myelodysplastic Syndromes. *N Engl J Med*. 2011;364(26):2496-2506.