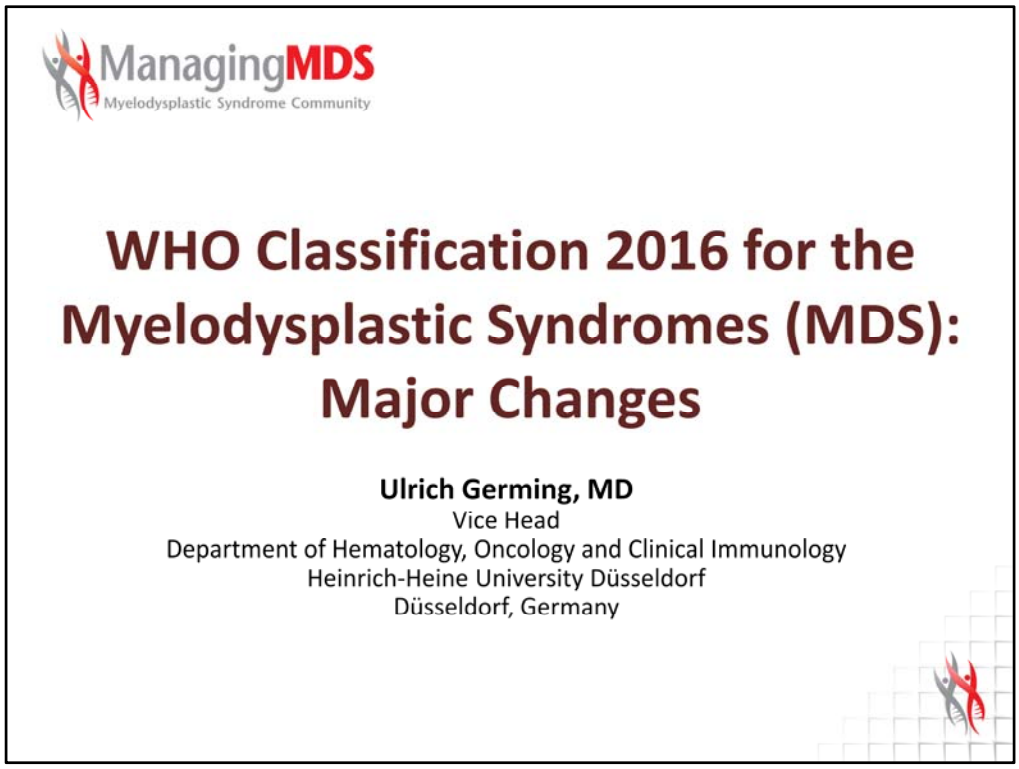
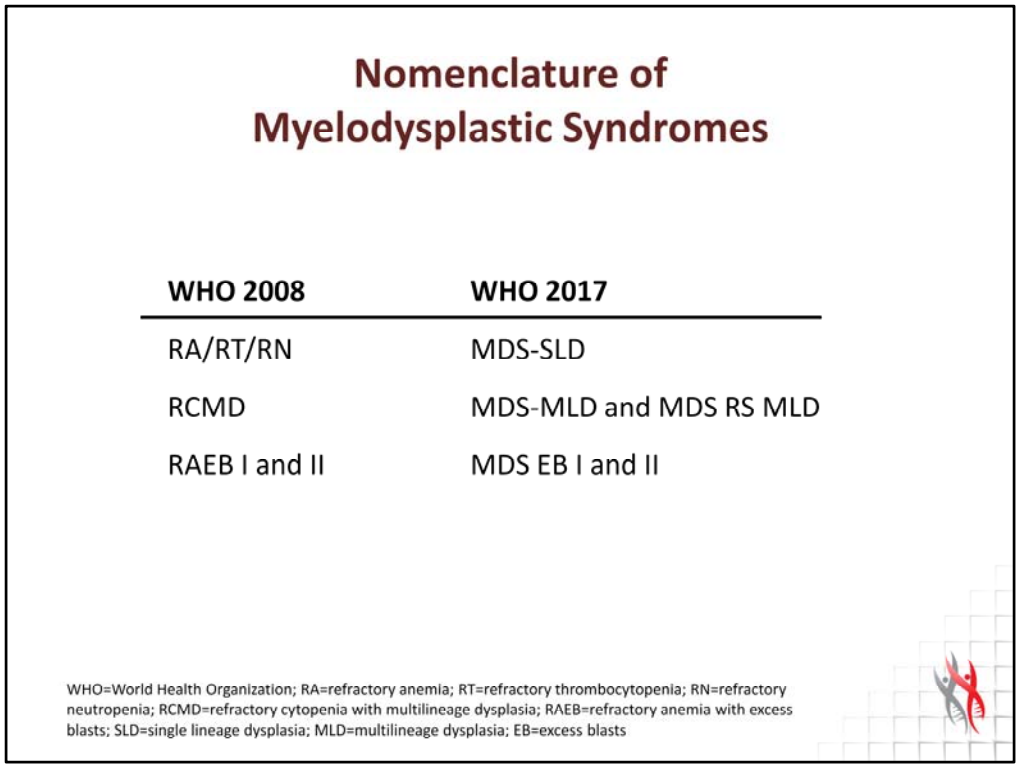
Changes to the 2016 WHO Classification for the Diagnosis of MDS



Welcome to *Managing MDS*. I am Dr. Ulrich Germing, and today, I will provide highlights from the 14th International Symposium on MDS in Valencia, Spain. My specialty is the diagnosis and prognosis of myelodysplastic syndromes, and I am a member of the WHO (World Health Organization) Clinical Advisory Committee.

I was involved in the development of classifications in 2008 and 2016 for the diagnosis of myelodysplastic and myelodysplastic/myeloproliferative syndromes. I want to share with you some highlights regarding the WHO classifications that were changed in 2016 because, in part, they are very important for correct diagnosis and finding the correct treatment for patients.

WHO Classification 2016 for the Myelodysplastic Syndromes (MDS): Major Changes



There are some steps to go through for the correct classification including the new nomenclature of the myelodysplastic syndromes. It was decided to have new names for the different MDS types, changing from describing just an anemia or neutropenia or thrombocytopenia, to including in the name what is happening in the marrow. The nomenclature changed from “refractory cytopenia” to “MDS single-lineage dysplasia” or “MDS multilineage dysplasia.” The term “refractory anemia with excess of blasts” was changed to “MDS excess of blasts I and II.” This takes into account the concentration on the dysplastic features in the marrow more than on what is happening in the peripheral blood. We have this new wording for the different types. This is the first major step, so we will have to get used to having the new correct terms when describing what is happening in the marrow.

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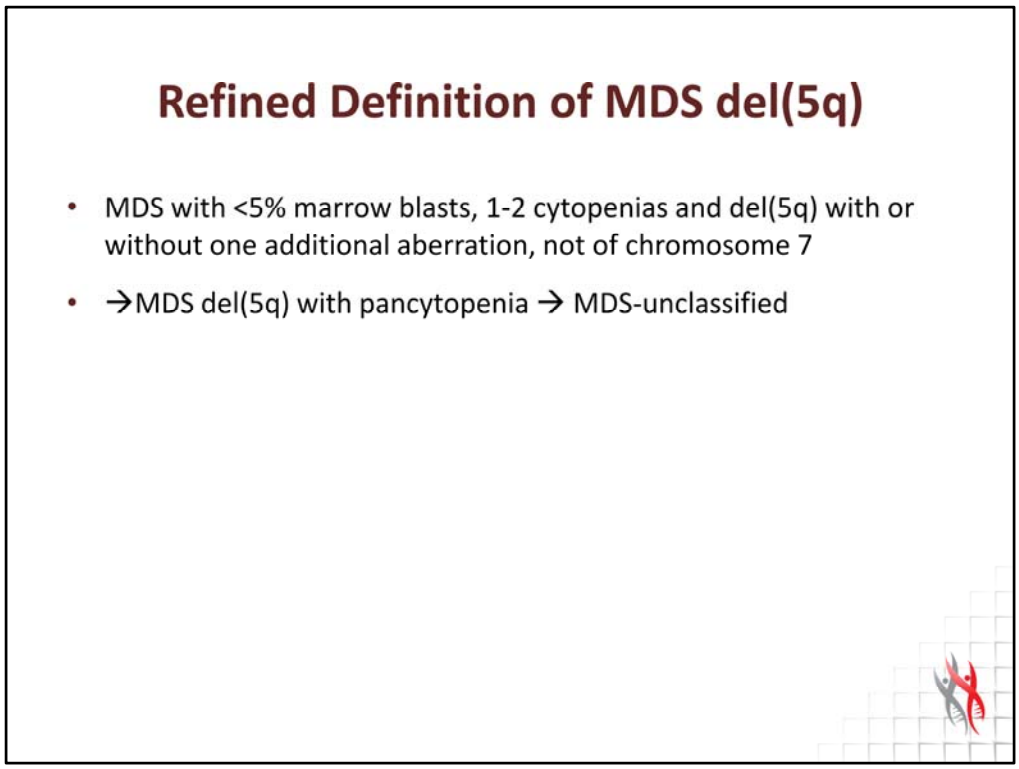

The second step that was changed is a new definition of some of the subtypes including the MDS del 5q. In former times, MDS del 5q was defined as having a patient without increased blast and blood in the marrow, with an isolated deletion of the long-arm of chromosome 5. For good reasons, this classification was changed a little bit. Patients who harbor the del 5q and have an additional aberration like –Y, trisomy 8, 20q-, or other aberrations are put into this category together with the others that have only del 5q isolated.

The reason for that is that one additional aberration does not alter the clinical cause of the disease. It does not alter the pathophysiological things that are going on in the blood and marrow, and it does not alter the clinical cause with regard to treatment with lenalidomide. The new entity also includes patients with one additional aberration, with one important exception. If the patient has aberrations of chromosome 7 together with the del 5q, this patient will not be placed into this category because chromosome 7 aberrations have a very poor prognosis, and so, they are separated and put into the MDS MRD category.

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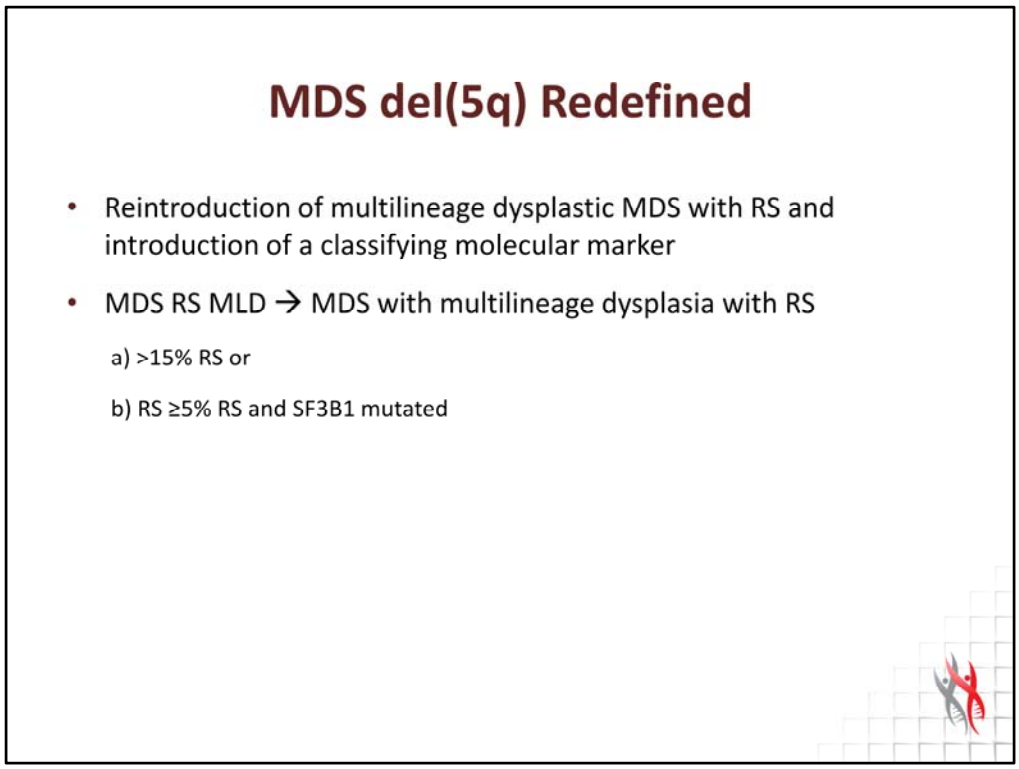

The third major change in the WHO 2016 classifications is that patients with ring sideroblastic anemia, either as a single-lineage dysplasia or multilineage dysplasia, are regarded as a separate entity. The reason for that is that a couple of years ago it was demonstrated very clearly that there is a somatic mutation of SF3B1 splicing factor III. Mutation was correlated with a ring sideroblastic phenotype of the myelodysplastic syndromes.

This point led the WHO to use the SF3B1 mutation as a classifying event. In other words, if you have a patient who has an MDS single-lineage dysplasia or multilineage dysplasia harboring SF3B1 mutation, the patient is placed into the category MDS ring sideroblastic phenotype multi- or single-lineage dysplasia. This is of special interest as, in the last couple of years, some TGF-ß blocking drugs obviously worked quite fine in patients harboring the SF3B1 mutations. It makes sense to have these entities separated.

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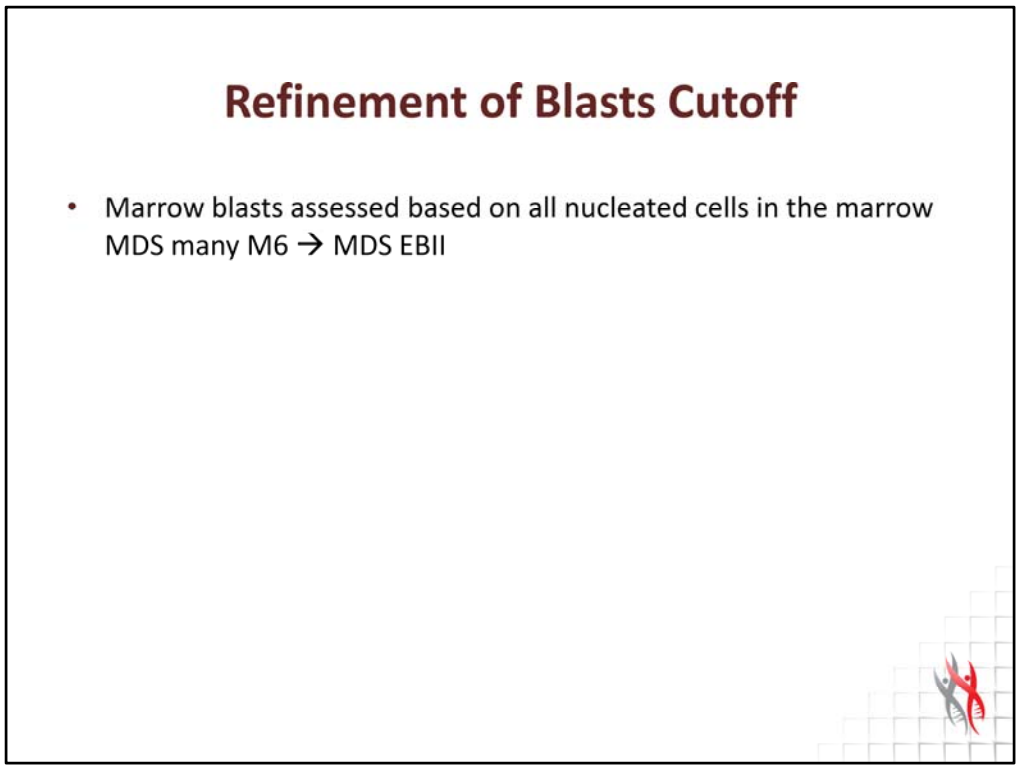

The fourth thing that was changed is also important. In former times, the medullary blast count (the leukemia cell count) was taken in the marrow on the basis of the non-erythroid lineage. That means if a vast majority of cells in the marrow are non-erythroid, you have a medullary blast count of 5%, 10%, 15%, or 20% leading to a diagnosis of an MDS without blast count excess, or to grade 1 or grade 2 type, or even to an AML. Now, the WHO decided to let the medullary blast count be assessed on the entire cell population of the marrow, not taking into account the amount of erythropoietic cells.

In other words, some of the AMLs that were defined formerly as an erythroid leukemia now jump into the category of grade 1 or grade 2; a new classification MDS EB1 and EB2. The major reason for this decision was that the patients with the erythroid leukemia behaved clinically, more or less, exactly as the MDS EB1 and EB2 types do. It was decided to lump these categories together by assessing the medullary blast count on the entire cell population.

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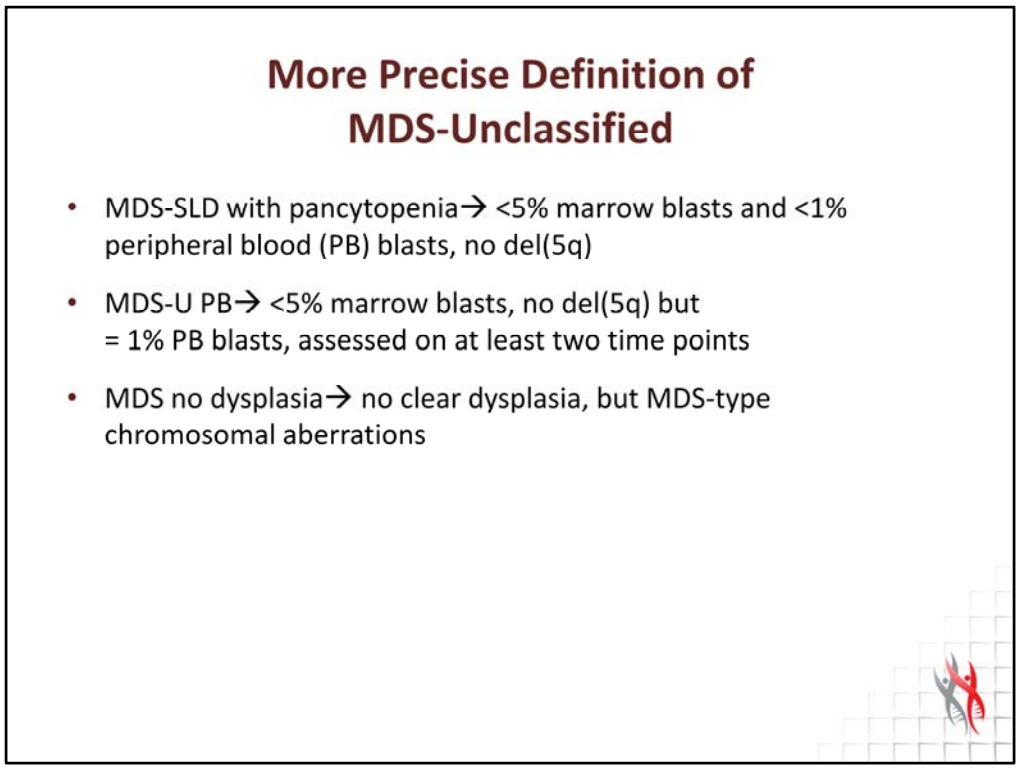

The fifth thing that was changed was a definition of three small categories called “MDS unclassified,” because they do not fit into the MDS single-lineage, multilineage EB1 and EB2 types. There are three conditions that may occur in a small number of patients leading to these MDS unclassified categories. The first one is patients who have single-lineage dysplasia in the marrow but show pancytopenia on peripheral blood. It is only a small number of patients but they exist, and those patients behave worse from the prognostic point of view, as compared to the other single-lineage dysplastic MDS. This is the category MDS unclassified with pancytopenia. The second MDS unclassified category are those patients who have 1% peripheral blast in the peripheral blood, not fitting into the categories of MDS single- or multilineage dysplasia. This category is also very infrequent, but some patients exist, and again those patients showing 1% peripheral blast have a poor prognosis. The third category of the MDS unclassified is the most interesting category. It includes patients who show only very, very mild signs of dysplasia in the marrow that is not enough to state this is an MDS, but those patients show chromosomal aberrations that are typical for myelodysplastic syndromes.

In other words, this diagnosis cannot be made by the hematologist or the pathologist, but by the cytogeneticist. They see for example, aberrations on chromosome 5 or 7 or other things that drive the attention of the hematologist to the fact that this is a clonal marrow not yet showing dysplastic features. This is of high importance because more and more patients that have only mild cytopenia and mild dysplasia undergo chromosomal aberrations or even molecular screening. Those patients harboring the clonal marrow have a way to develop myelodysplastic syndrome or even acute myeloid leukemia, but it is not enough to state yes this is MDS or AML by means of histopathology or cytology. This new category was defined, and it is very helpful because you can collect patients with this clonal marrow on the way to developing myelodysplastic syndromes.

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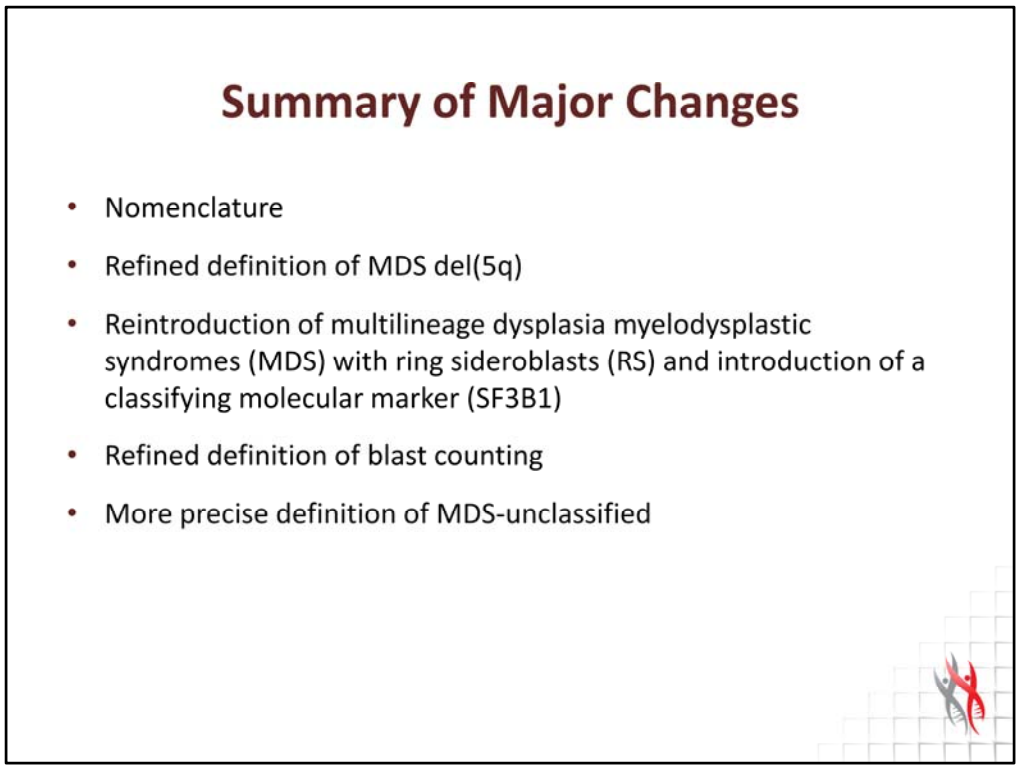

These are the major changes that we have to take into account when diagnosing myelodysplastic syndromes either by pathologists (in the United States) or the hematologists (for example in Germany).

Summing up, it is the nomenclature that changed, the new definition of del 5q, the reintroduction of the ring sideroblastic phenotype using the SF3B1 mutation, the new assessment of the medullary blast count, and finally the definitions of the MDS unclassifiable categories. Thank you for your attention.

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