Aging, CHIP and MDS

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Welcome to *Managing MDS*. I am Dr. David Steensma from the Dana-Farber Cancer Institute in Boston. Today, I will be providing some highlights from my lecture at the 14th International Symposium on Myelodysplastic Syndromes (MDS) in Valencia, Spain. My presentation was about aging, CHIP, and MDS. What is CHIP? For those who are not familiar, this stands for clonal hematopoiesis of indeterminate potential; more about that in a moment. I talked about aging and the different physiologic changes that occur during aging. Some of these are quite predictable.

In the 40s, we lose our ability to accommodate visually and start to need progressive lenses or bifocals. Our wrinkles start to appear. Our maximum heart rate on the treadmill at the gym starts to slowly slide down as we get older. Many of these changes are internal, things like decreased lung capacity or decreased renal filtration. Those that are of most interest to the hematologist have to do with the changes in the marrow that occur over time. We all know as hematologists that the marrow becomes fattier over time, and in fact, the cellularity of the marrow is benchmarked to age. For a 70-year-old person, a 30% cellular marrow, that is 70% fat, would be normal. That would be abnormal for a 30-year-old person where the marrow should be 30% fat, give or take 10%, and 70% hematopoietic elements. As the marrow changes with aging, there are all sorts of different alterations that occur.

The differentiation program for progenitor cells, for instance, moves more toward adipocyte development and less toward development of hematopoietic elements. Among hematopoietic elements, development shifts toward common myeloid progenitors. The total number of hematopoietic stem cells giving rise to hematopoiesis diminishes, and there are a number of other changes as well. It is basically senility of the bone marrow. One of the things that happens with aging is development of clonal states, for instance, monoclonal gammopathies of undetermined significance which are a risk factor for plasma cell myeloma and for other plasma cell disorders. Monoclonal B-cell lymphocytosis of undetermined significance becomes very common after age 65 to 70 years, and this is a risk factor for development of either CLL or non-Hodgkin lymphoma.

In the last few years, we have learned that many patients who have normal blood counts develop clonal mutations in putative leukemia driver genes, especially DNMT3A and TET2, less commonly TP53, SF3B1, and others. There is, just as for monoclonal

gammopathy of undetermined significance (MGUS), a risk for these patients to progress from the clonal preneoplastic state to overt malignancy. The same is true for these clonal mutations. The rate of progression is about the same for MGUS to myeloma, 0.5% to 1% per year, as it is for CHIP to MDS or leukemia, also about 0.5% to 1% per year. There are several other factors that are of special interest with respect to CHIP. Number one, CHIP is a risk factor for cardiovascular outcomes. We do not exactly understand why this is. There have been some new mouse models that have been published just in the last few months that have suggested TET2 clones can interact with the vascular endothelium to accelerate atherogenesis and increase the risk for a stroke or heart attack. There may also be a common risk factor for developing clonal hematopoiesis and accelerated atherogenesis. However, this is quite a significant public health issue because 10% of individuals over age 70, and by age 85, one-third of the population, will have CHIP. It is a risk factor for cardiovascular disease of the same order of magnitude as cigarette smoking or high cholesterol. Imagine if we could intervene in this, imagine if we could eliminate clonal hematopoiesis. Potentially, we could decrease not only hematological mortality, but cardiovascular mortality as well. In addition, CHIP highlights some of the challenges that we have with respect to diagnosis of MDS in its earliest phases.

I made an analogy in my presentation to the difference between nighttime and twilight. Right now, we are diagnosing MDS when it is already nighttime, when the sun is effectively 18 degrees below the horizon, but there are different degrees of twilight that occur after sunset. There is civil twilight, where the sun has gone down but it is still bright enough to read without artificial lighting. There is nautical twilight, where you cannot read anymore without artificial lighting but where you can still distinguish the horizon, and so you could potentially take a sight if you are on the boat with a sextant. Then lastly, there is astronomical twilight, that is where you can no longer discern the horizon, but it is still not as dark as it should be for viewing the dimmest stars. Of course, once the sun moves further down below the horizon, then we have true nighttime, true dark. I think the same is true of clonal hematopoiesis and myelodysplastic syndromes. By the time severe cytopenias occur, extensive cellular dysplasia, increased blasts, abnormal chromosomes, there is no subtlety about the diagnosis of MDS. We often see patients who have mild cytopenias, they do not have enough dysplasia to meet World Health Organization criteria for MDS. They do not have an increase in blasts. The karyotype is normal. Some of them do have clonal mutations and some do not. Where do we draw the line between what is MDS and what is not? Largely that line should be drawn based on the natural history of these various states.

Luca Malcovati and his colleagues in Italy recently published a very nice dataset in *Blood* where those patients who have cytopenias and clonal mutations are at much higher risk for going on to develop overt MDS, AML, and dying compared to those who have cytopenias and no clonal mutation. These patients with cytopenias plus a clonal mutation are sometimes called CCUS (clonal cytopenias of undetermined significance) because some of them do not go on to get MDS or AML, but most of them, over time, will.

So, CHIP is a cardiovascular risk factor. CHIP is common with aging. In fact, some groups have called it age-related clonal hematopoiesis, but it is not an inevitable consequence of aging, so that is why we prefer the term CHIP. CHIP may help, or at least the presence of clonal mutation, in distinguishing what is MDS from what is not MDS, but I think ultimately what we really need is some way to prevent CHIP from evolving. Our current drugs available for MDS are quite blunt instruments. Our myeloma colleagues are studying monoclonal gammopathy of undetermined significance and smoldering myeloma and they are trying to prevent progression to overt myeloma with daratumumab, elotuzumab, earlier use of lenalidomide, etc. We need better drugs for MDS so that we can prevent that progression, as well to potentially decrease cardiovascular mortality, if we can restore polyclonal hematopoiesis.

That is what I spoke about: aging, CHIP, and MDS. I also discussed that aging in some respects is so predictable. A few years ago, I went to the Minnesota State Fair, and there was a guy there who had a booth setup for “The Guesser” and you could pay $3 and he would guess your age within 2 years. If he was wrong, you got to pick a prize, a teddy bear or some other $2 trinket. If he guessed right, then you did not get anything. You can see how the economics work, if you had to pay $3 for the chance to win a $2 prize. Nonetheless, he was quite accurate at predicting peoples' age. There are also some changes that are not inevitable consequences of aging and CHIP is one of those, as is myelodysplastic syndrome. Thanks for your attention.