What are the recent insights into therapy-related MDS?

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Welcome to *Managing MDS*. I am Dr. Richard Larson. I am frequently asked, “What are the recent insights into therapy-related MDS?” We have known for several decades that individuals exposed to radiation, either environmental or therapeutic, or to DNA damaging chemotherapy drugs, have an increased risk of developing a therapy related myeloid neoplasm. In fact, this subtype has been defined by the World Health Organization as a distinct entity. This includes patients who have received any sort of DNA damaging agent and is not limited by the interval from exposure or the intensity of exposure. The purpose of this is to highlight the increasingly frequent appearance of these patients after successful treatment for a primary cancer, or an autoimmune disorder. In fact, at the University of Chicago, approximately 20% of the newly diagnosed MDS and leukemia patients that we see have had exposure to prior chemotherapy and/or radiation therapy. We would like to identify these patients to learn more about the mutagenic effects of these agents on humans and to discover the pathways for developing leukemogenesis, which will likely inform us about the development of de novo leukemia and MDS as well. Some of the areas of confusion and debate surrounding the definition of therapy-related leukemia have to do with what exposures are leukemogenic. Here we would include principally the alkylating agents as well as the topoisomerase II inhibitors such as etoposide, Adriamycin (doxorubicin), or mitoxantrone. More recently, evidence has come forward that antimetabolite therapy, for example purine antimetabolites like azathioprine, increase the risk of developing a therapy-related myelodysplasia or leukemia. Finally, radiation therapy, particularly to areas of the body that contain active bone marrow, such as the pelvis or the spine, sternum, and ribs, has been associated with the development of therapy-related myeloid neoplasia.

In general, there are two presentations that we see. One is with a more smoldering myeloid neoplasm, which is very similar to MDS de novo. These patients often have received alkylating agents, and the latency interval from first exposure on average is about 5 to 7 years. They are characterized by complex cytogenetic abnormalities, often including abnormalities of chromosome 5 or 7. A second subtype of therapy related myeloid neoplasia includes patients who were exposed to topoisomerase II inhibitors such as etoposide or Adriamycin or sometimes radiation therapy as the sole abnormality. These patients often present with a more proliferative myeloid neoplasm and acute myeloid leukemia that is characterized by balanced translocations such as translocation 8;21 or an inversion 16 or translocations 15;17, very similar to what is observed in de novo acute promyelocytic leukemia. Here, the latency period is often

considerably shorter, perhaps only 1 to 3 years from first exposure to these cytotoxic agents. Currently, these leukemias and myelodysplastic disorders are being explored at a genetic level. Interestingly, the mutated genes that are more commonly seen in de novo leukemia, such as mutations in FLT3 or NPM1 or C/EBP alpha are rarely seen in patients who develop therapy related myelodysplasia or leukemia. In contrast, more often we see mutations in TP53 or genes involved in the epigenetic pathways, such as TET2, ASXL1, or EZH2. Eventually, I think these genetic studies will inform us about who is at risk for therapy-related leukemia. It is certainly possible that these myeloid malignancies develop as a stochastic abnormality or purely by chance. Alternatively, there may be a mutational event or series of mutational events that lead to therapy-related MDS, or there may be selection for a mutator phenotype which may be the mechanism of leukemogenesis seen with azathioprine, for example. There may also be germline genetic abnormalities which increase the likelihood that specific patients may not tolerate chemotherapy well and develop a therapy-related myelodysplasia. These could be hereditary cancer susceptibility genes, such as mutations in TP53 or BRCA1 or BRCA2 or the Fanconi genes or inactivating polymorphisms in the metabolic pathways that deactivate certain chemotherapy drugs. Finally, there may be increased risk of developing therapy-related MDS or myeloid leukemia in subjects1, who have inherited familial predisposition to developing myeloid leukemias, such as mutations in RUNX1, C/EBP alpha, or telomerase genes, for example. I think that there will be increasing focus on this subset of patients who present with either MDS or myeloid leukemia that is very much skewed toward the high risk end of the spectrum that we see for myeloid neoplasms. Thank you for viewing this activity.