

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Susceptibility to Therapy-related Myelodysplastic Syndromes and Acute Myeloid Leukemia

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H&O What is the definition of therapy-related myelodysplastic syndromes and acute myeloid leukemia?

HS According to the World Health Organization classification, therapy-related myelodysplastic syndromes and acute myeloid leukemia (t-MDS/t-AML) are secondary neoplastic disorders occurring as a late consequence of prior cytotoxic therapy, in general chemotherapy and/or radiotherapy. In recent years, the therapeutic use of recombinant growth factors like the granulocyte colony-stimulating factor has also been described as a risk factor for t-MDS/t-AML. However, as there are no specific genetic markers for t-MDS/t-AML, it is impossible to determine with certainty whether myelodysplasia (MDS) or acute myeloid leukemia (AML) occurring after a primary disorder is the result of previous therapies or might also have developed spontaneously.

H&O What was the historical understanding of t-MDS/t-AML?

HS t-MDS/t-AML were first described in the 1960s and early 1970s when an association between chemotherapy and/or radiotherapy and the development of (pre-)leukemia was recognized. Among the best-evaluated entities in this setting are non-Hodgkin lymphomas. In these disorders, clinical risk factors for developing t-MDS/t-AML include patient's age at the time of primary therapy, the number of chemotherapy/radiotherapy cycles given

for the primary malignancy, and the inclusion of total body irradiation. It remains a matter of debate whether autologous stem cell transplantation per se adds to the risk of t-MDS/t-AML. Epidemiologic study designs that are most suitable for evaluation of t-MDS/t-AML risk are cohort studies based on population-based cancer registries or large clinical trial databases.

H&O What are the directions of research into understanding the genetic basis of t-MDS/t-AML?

HS t-MDS/t-AML arise in a small but significant proportion of patients after cytotoxic therapies, with a crude incidence between less than 1% and 15%. In those individuals who develop t-MDS/t-AML, an abnormal response of hematopoietic stem cells to the primary therapy has to be postulated. Although the etiology of t-MDS/t-AML is most likely multifactorial, genetic predisposition may form the basis of such an abnormal response.

One strategy for understanding the etiology of t-MDS/t-AML is based on familial syndromes with an increased risk of primary and secondary malignancies. Patients with neurofibromatosis type 1 (NF1) are not only at risk for de novo myelomonocytic leukemias but have also been reported to develop t-AML. In some of these individuals who exhibit features of NF1 and suffer from hematologic malignancies, germline mutations in the DNA mismatch repair genes *MLH1* and *MSH2* have been described.

Animal studies are another valuable tool to explore predisposition to t-MDS/t-AML. Mice genetically modified for the *NF1* gene were treated with cyclophosphamide—one of the most commonly used alkylating agents in humans—and radiation. In comparison with wild-type mice, heterozygous animals developed more secondary tumors, including myeloid leukemias. These animal data provide strong evidence for genetic predisposition to therapy-related malignancies and represent a model for

investigating the carcinogenic potential of different anti-neoplastic regimens.

Finally, studying affected patients may provide insight into mechanisms of predisposition to t-MDS/t-AML. Several investigations have focused on polymorphisms within genes encoding drug metabolism and DNA repair pathways, respectively. The case-control study is thereby a widely used study design comparing t-MDS/t-AML patients with either healthy controls or patients with de novo MDS/AML. However, these studies require caveats with respect to their control group, statistical power, or functional relevance of the polymorphisms investigated. Recently, two transforming germline mutations of the *C-RAF* proto-oncogene have been described in patients with t-AML. As the RAF/MEK/ERK pathway has been shown to be activated in both the primary tumor and the t-AML, these mutations might contribute to the development of both neoplasias.

H&O What is the clinical relevance and outlook of these discoveries regarding genetic predisposition?

HS t-MDS/t-AML are malignancies highly resistant to conventional therapies. Survival of an unselected cohort of t-MDS/t-AML patients is less than 10% at 5 years. The only curative approach is allogeneic stem cell transplantation, which is applicable to a minority of these patients and characterized by high transplant-related mortality.

The concept of predisposition could be translated into identifying patients at high risk of developing t-MDS/t-AML at the time of the primary therapy. If this hypothesis holds true, it might be possible to offer patients alternative treatment strategies, thereby reducing the risk of t-MDS/t-AML. However, it is likely that such an approach is applicable to certain subgroups rather than to the entire cohort of patients receiving cytotoxic therapies. One example is found in preliminary results in prostate cancer where two equivalent treatment strategies—operation and radiotherapy—are available. After a large cohort of patients had been followed, it could be shown that those who had received radiotherapy had a greater risk of developing AML. Being able to assess susceptibility to t-AML in this group of patients may therefore represent a tool for t-AML prevention.

H&O Are there other strategies for identification of genetic risk factors?

HS Yes. One possibility might be to search for germline mutations of candidate genes within pathways activated during leukemogenesis. Another strategy could utilize whole-genome scanning array-based technologies to identify novel disease-associated loci. However, this approach would require large numbers of uniformly treated patients. Finally, families of t-MDS/t-AML patients sometimes demonstrate a high incidence of solid and hematologic malignancies. Exploration of these families might also lead to novel insights into predisposition to t-MDS/t-AML.

Suggested Readings

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