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Editorial

Introduction to a review series on secondary leukemia

The term secondary acute myeloid leukemia (sAML) is today employed to indicate AML or myelodysplastic syndrome (MDS) evolving from a preexisting hematologic disorder, whereas AML or MDS that develops after exposure to chemotherapy or radiotherapy is referred to as therapy related (t-AML). Overall, the increasingly recognized, heterogeneous sAML pathogenic spectrum may account for 10% to 30% of all cases of AML or MDS, but this varies from study to study, given the heterogeneity and poor definition of the term. In addition, it is thought that a fraction of AML cases presenting as de novo may be secondary in nature with regard to ontogeny.[1]

In this series, we highlight sAML occurring in several groups of genetic or acquired, benign or malignant, hematologic disorders. The nonexhaustive series includes the following review articles:

- Anna L. Brown, Christopher N. Hahn, and Hamish S. Scott, "Secondary leukemia in patients with germline transcription factor mutations (*RUNX1*, *GATA2*, *CEBPA*)"
- Lova Sun and Daria V. Babushok, "Secondary myelodysplastic syndrome and leukemia in acquired aplastic anemia and paroxysmal nocturnal hemoglobinuria"
- Andrew J. Menssen and Matthew J. Walter, "Genetics of progression from MDS to secondary leukemia"
- Andrew J. Dunbar, Raajit K. Rampal, and Ross Levine, "Leukemia secondary to myeloproliferative neoplasms"

Recent progress in the understanding of sAML owes much to the insights provided by clinical, cytogenetic, and genomic studies. Although widely disparate in their background and natural history, sAML (and t-AML) cases often present with common features compared with de novo (eg, CBF, PML-RARA, or NPM1 associated) AML. These can include unfavorable prognosis, lower blast cell infiltration and frequent myelodysplastic morphology in the bone marrow, and chromosomal or molecular lesions such as monosomy 7/del(7q), *TP53* mutations/deletions, and complex karyotype. At the functional level, pathways involved in regulating apoptosis, DNA damage response, cell signaling, chronic inflammation, and innate immunity may participate to shape progression in the context of altered hematopoiesis. There is a strong need to better understand the intrinsic and extrinsic clues underlying stepwise progression toward overt sAML and set up predictive biomarkers to promptly treat patients, ideally in a preemptive manner and according to evidence-based guidelines. For this purpose, more data on the natural history of the disease from meticulously annotated patient cohorts and longitudinal samples are needed, as are clinical trials as well as in vitro and in vivo experimental and preclinical models.

We hope that this series will provide useful insights into sAML, a dramatic evolution of disease that is concerning for patients and their physicians.

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REFERENCE

1. Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood*. 2015;125(9):1367-1376.

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