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| CLINICAL Utility of Molecular Testing in  MYELOID NEOPLASMS POST CYTOTOXIC THERAPY  Diagnostic Utility  Myeloid neoplasms post cytotoxic therapy (MN-pCT) encompass myelodysplastic neoplasms (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and acute myeloid leukaemia (AML) that arise in a patient with a history of exposure to DNA-damaging cytotoxic chemotherapy and/or large-field radiation therapy1.  In contrast to the WHO 5th edition, the international consensus classification (ICC) of myeloid neoplasms and acute leukaemia has eliminated a stand-alone category of MN-pCT and instead “therapy-related” is applied as a secondary diagnostic qualifier to be used following a specific MDS, AML (or MDS/AML) diagnosis2.  *TP53* mutations (frequently multi-hit), along with del(5q), -7/del(7q) and a complex karyotype are significantly over-represented in MN-pCT and are associated with prior alkylating therapy and/or ionizing radiation1,3.  Recurrent balanced translocations, frequently involving 11q23 (*KMT2A*)*,* are associated with prior topoisomerase II inhibitor therapy, a short latency period and presentation with overt AML without a preceding MDS phase4.  Other gene mutations more frequently observed in MN-pCT include *PPM1D* (~15%) and other DNA damage response genes5,6.  Exposure to PARP1 inhibitors is now recognised as a qualifying criterion for MN-pCT, while methotrexate exposure has been excluded1.  MN-pCT generally arise within 10 years of last exposure to cytotoxic therapy, and the origin of cases with very long latency periods may be unrelated to therapy7.  A subset of MN-pCT patients, especially those with a strong family history of cancer, may have inherited germline mutations in genes involved in DNA damage response pathways3.  A subset of AML-pCT have secondary-type mutations (*SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1, EZH2*,or *STAG2*) which resemble AML, myelodysplasia-related (AML-MR) following a known history of MDS or MDS/MPN8.  Prognostic Utility  Whilst the prognosis of patients with t-MN is generally poor, patients with complex karyotype, abnormalities of chromosomes 5 and/or 7 and TP53 mutations have particularly inferior outcomes.  References  1. Khoury JD, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022. 2. Arber DA, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data. Blood 2022. 3. McNerney ME, et al. Therapy-related myeloid neoplasms: when genetics and environment collide. Nat Rev Cancer 2017; 17(9): 513-27. 4. Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, editor. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. 5. Wong TN, et al. Cellular stressors contribute to the expansion of hematopoietic clones of varying leukemic potential. Nat Commun 2018; 9(1): 455. 6. Coombs CC, et al. Therapy-Related Clonal Hematopoiesis in Patients with Non-hematologic Cancers Is Common and Associated with Adverse Clinical Outcomes. Cell Stem Cell 2017; 21(3): 374-82 e4. 7. Østgård LSG, et al. Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. J Clin Oncol 2015; 33(31): 3641-9. 8. Lindsley RC, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood 2015; 125(9): 1367-76. |