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| cLINICAL UTILITY OF MOLECULAR TESTING IN  Acute Leukaemias of Ambiguous Lineage  DIAGNOSTIC utility  Acute leukaemias of ambiguous lineage (ALAL) are a group of rare, high-risk leukaemias encompassing acute undifferentiated leukaemia (AUL) and mixed phenotype acute leukaemia (MPAL)1.  The diagnosis of ALAL currently relies on immunophenotyping. The finding of recurrent gene rearrangements (not detected by this assay) can help refine subclassification (see below) and also exclude other WHO-defined entities such as acute myeloid leukaemia (AML) with t(8;21)(q22;q22.1); *RUNX1::RUNX1T1* and myeloid/lymphoid neoplasms with *FGFR1* rearrangement1.  The most common recurrent chromosomal aberrations identified in MPAL and which define distinct MPAL subtypes in the 2016 WHO are t(9;22)(q34.1;q11.2); *BCR::ABL1* and t(v;11q23); *KMT2A*-rearranged, both typically associated with a B/myeloid phenotype1.  *ZNF384* rearrangement occurs in approximately 50% of paediatric B/myeloid MPAL2. While the rearrangement is uncommon in adult MPAL, it may also be observed in both adult and paediatric B-lymphoblastic leukaemia (commonly in cases with aberrant myeloid antigen expression)2-4. A number of other recurrent gene rearrangements have been described2,5.  While T/myeloid and B/myeloid MPAL have overlapping genomic profiles, *NOTCH1* mutations are not typically observed in B/myeloid MPAL4,6.  T/myeloid MPAL and early T-cell precursor ALL (ETP-ALL) share a number of genomic features. Commonly mutated genes in T/myeloid MPAL include transcriptional regulators such as *WT1*, *ETV6*, *RUNX1* and *CEBPA*,signalling pathway genes(*FLT3*, *NRAS*, *KRAS*)and epigenetic modifiers (*DNMT3A*, *TET2*, *IDH1*, *IDH2* and inactivating *EZH2* mutations)2,4,6.  Recurrently mutated genes in B/myeloid MPAL include transcriptional regulators (*RUNX1*, *WT1*, *PAX5*, *ETV6*), *FLT3* and RAS signalling genes (*NRAS*, *KRAS*, *PTPN11*)2,7. Copy number alterations affecting genes such as *IKZF1* may also be observed (not detected by this assay).  *TP53* mutations have been observed in both T/myeloid and B/myeloid MPAL2,6.  *NPM1* mutations are specific to AML and have not been found in MPAL2,4.  BIOMARKERS OF RESPONSE TO THERAPY  Tyrosine kinase inhibitor therapy in combination with chemotherapy is recommended for MPAL with t(9;22)(q34.1;q11.2); *BCR::ABL18,9*.  *FLT3* (TKD and ITD) and *IDH1* and *IDH2* mutations are the target of FLT3 and IDH inhibitors, respectively; however, data are limited in ALAL10,11.  REFERENCES  **1.** Swerdlow S, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **2.** Alexander TB, et al. The genetic basis and cell of origin of mixed phenotype acute leukaemia. *Nature* 2018; **562**(7727): 373-9. **3.** Liu Y-F, et al. Genomic Profiling of Adult and Pediatric B-cell Acute Lymphoblastic Leukemia. *EBioMedicine* 2016; **8**: 173-83. **4.** Takahashi K, et al. Integrative genomic analysis of adult mixed phenotype acute leukemia delineates lineage associated molecular subtypes. *Nat Commun* 2018; **9**(1): 2670. **5.** Montefiori LE, et al. Enhancer Hijacking Drives Oncogenic BCL11B Expression in Lineage-Ambiguous Stem Cell Leukemia. *Cancer Discov* 2021; **11**(11): 2846-67. **6.** Eckstein OS, et al. Mixed-phenotype acute leukemia (MPAL) exhibits frequent mutations in DNMT3A and activated signaling genes. *Exp Hematol* 2016; **44**(8): 740-4. 7. Cao P, et al. Deciphering Common Gene Fusions and Mutations in Acute Leukemia of Ambiguous Lineage. Blood 2019; 134(Supplement\_1): 3793-. 8. Shimizu H, et al. Philadelphia chromosome-positive mixed phenotype acute leukemia in the imatinib era. European Journal of Haematology 2014; 93(4): 297-301. 9. Wolach O, Stone RM. How I treat mixed-phenotype acute leukemia. Blood 2015; 125(16): 2477-85. 10. Patel SH, et al. Molecular Complete Remission Following Ivosidenib in a Patient With an Acute Undifferentiated Leukemia. J Natl Compr Canc Netw 2020; 18(1): 6-10. 11. Tremblay Z, et al. Use of midostaurin in mixed phenotype acute leukemia with FLT3 mutation: A case series. European Journal of Haematology 2022; 108(2): 163-5. |