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| cLINICAL UTILITY OF MOLECULAR TESTING IN chronic myeloid leukaemia  DIAGNOSTIC utility  Chronic myeloid leukaemia (CML) is characterised by the reciprocal translocation t(9;22)(q34.1;q11.2), resulting in the *BCR-ABL1* fusion gene.  The p210 BCR-ABL1 fusion protein (p210) is detected in the vast majority of CML cases, encoded by either e13a2 (b2a2) or e14a2 (b3a2) fusion transcripts, or both1.  Rarely, a larger p230 fusion protein (p230) is encoded, characterised by prominent neutrophilic maturation and/or thrombocytosis2.  The p190 fusion protein (p190), resulting from the fusion transcript e1a2, is most frequently associated with Ph-positive ALL, however it occurs as the sole BCR-ABL isoform at diagnosis in a minority of CML cases (1-2%) and has been associated with monocytosis3. The p190 may also be co-expressed at low levels with p2104.  Monitoring of the *BCR-ABL1* transcript is crucial to ensure achievement of on-therapy milestones including 3 (≤10%), 6 (<1%), and 12 months (≤0.1%), as well as assessing eligibility for treatment discontinuation, and to detect loss of major molecular remission during treatment-free remission5.  The detection of two or more mutations in the *BCR-ABL1* fusion gene during tyrosine kinase inhibitor (TKI) therapy is one of the WHO provisional criteria for accelerated phase CML6.  Non-*BCR-ABL1* mutations in other genes are observed in a proportion of chronic phase CML patients, including *ASXL1, TET2*, and *DNMT3A*7-9, but are also observed in clonal haematopoiesis of indeterminate potential (CHIP)10.  In additional to karoytypic abnormalities, mutations may be detected in blast phase CML including *BCR-ABL1* kinase domain mutations (45%), *RUNX1 (*15-20%), *ASXL1* (15-20%), and *IKZF1* (deletion or mutation)7,11,12.  BIOMARKERS OF RESPONSE TO THERAPY  The *BCR-ABL1* oncoprotein is the target of TKIs13-15.  Acquired point mutations in the kinase domain of *BCR-ABL1* are a common cause of resistance to tyrosine kinase inhibitors5,16,17. With superior detection sensitivity, NGS (performed on cDNA) is now recommended over Sanger sequencing for detection of *BCR-ABL1* resistance mutations in patients not responding adequately to TKI5.  Specific *ABL1* mutations have differing reported sensitivities to available TKIs and these should be considered when selecting a TKI18.  Ponatinib is an effective TKI for CML with an *ABL1* Thr315Ile (*BCR-ABL1*T315I) mutation which confers resistance to both nilotinib and dasatinib19.  REFERENCES  1. Benjamin H, et al. Distinct characteristics of e13a2 versus e14a2 BCR-ABL1 driven chronic myeloid leukemia under first-line therapy with imatinib. Haematologica 2014; 99(9): 1441-7. 2. Pane F, et al. Neutrophilic-chronic myeloid leukemia: a distinct disease with a specific molecular marker (BCR/ABL with C3/A2 junction). Blood 1996; 88(7): 2410-4. 3. Melo JV, et al. P190BCR-ABL chronic myeloid leukaemia: the missing link with chronic myelomonocytic leukaemia? Leukemia 1994; 8(1): 208-11. 4. van Rhee F, et al. p190 BCR-ABL mRNA is expressed at low levels in p210-positive chronic myeloid and acute lymphoblastic leukemias. Blood 1996; 87(12): 5213-7. 5. Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020; 34(4): 966-84. 6. Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. 7. Adnan-Awad S, et al. Mutational landscape of chronic myeloid leukemia: more than a single oncogene leukemia. Leukemia & Lymphoma 2021; 62(9): 2064-78. 8. Nteliopoulos G, et al. Somatic variants in epigenetic modifiers can predict failure of response to imatinib but not to second-generation tyrosine kinase inhibitors. Haematologica 2019; 104(12): 2400-9. 9. Kim T, et al. Spectrum of somatic mutation dynamics in chronic myeloid leukemia following tyrosine kinase inhibitor therapy. Blood 2017; 129(1): 38-47. 10. Jaiswal S, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014; 371(26): 2488-98. 11. Adnan Awad S, et al. Mutation accumulation in cancer genes relates to nonoptimal outcome in chronic myeloid leukemia. Blood Adv 2020; 4(3): 546-59. 12. Grossmann V, et al. A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases. Leukemia 2011; 25(3): 557-60. 13. O'Brien SG, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003; 348(11): 994-1004. 14. Saglio G, et al. Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. New England Journal of Medicine 2010; 362(24): 2251-9. 15. Kantarjian H, et al. Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. New England Journal of Medicine 2010; 362(24): 2260-70. 16. Jabbour E, et al. Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. Leukemia 2006; 20(10): 1767-73. 17. Shah NP, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell 2002; 2(2): 117-25. 18. Branford S, et al. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? Blood 2009; 114(27): 5426-35. 19. Cortes JE, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013; 369(19): 1783-96. |