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Acute Leukemias

CT-DNA-BASED LIQUID BIOPSY OF CEREBROSPINAL FLUID IN AN ADULT WITH MENINGEAL RELAPSE OF ACUTE LYMPHOBLASTIC LEUKAEMIA PH+

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Introduction: Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) accounts for approximately 25% of ALL cases in adults. It typically presents with an aggressive clinical course, but the integration of tyrosine kinase inhibitors (TKIs) into chemotherapy regimens has allowed a notable increase in remissions. Despite the significant progress, some patients relapse in the central nervous system (CNS) after treatment, due to the low blood–brain barrier permeability of TKIs. Currently, CNS relapse monitoring is performed by conventional imaging techniques and cytology analysis of the cerebrospinal fluid (CSF). However, these techniques have limited sensitivity. We describe the usefulness, in terms of non-invasiveness and sensitivity, of cell-free tumor DNA testing (Liquid Biopsy, LB) on CSF in a patient with Ph-positive ALL (M-BCR: BCR-ABL p210 b3a2 transcript) who developed a meningeal recurrence after imatinib-based treatment.

Methods: The patient was a 75 year old man with a story of Ph+ LLA, with Complete Hematologic Remission for >5 years. After the development of headache, brain MRI, lumbar puncture and minimal residual disease (MRD) testing on peripheral blood were requested for suspected CNS relapse.

Follow-up of (MRD) on peripheral blood was carried out with one-step Real-Time PCR monitoring of the BCR-ABL p210 b3a2 transcript on RNA extracted from buffy coat and with Philadelphia chromosome FISH.

Free circulating DNA and RNA were extracted from a sample of CSF to investigate the presence of relapses in the central nervous system and to characterize it from a molecular point of view. The molecular research was conducted through the Next-Generation Sequencing (NGS) analysis, with Ion Torrent technology, of a myeloid panel which simultaneously interrogates 45 DNA target genes and 35 fusion driver genes (RNA).

Results: Brain MRI revealed enhancement areas in the subarachnoid space. Lumbar puncture showed high opening pressure an increased cell count, with 468 cells / µL with 51% blasts.

FISH and Real-Time PCR on peripheral blood had low positivity (ratio BCR/ABL x 100 (IS) = 0.013%), consistent with complete hematological response. Conversely, Real-Time PCR on CSF was positive, with an imbalance score of 0.0002% for the BCR::ABL1B13A transcript, consistent with brain relapse.

Real-Time PCR quantitative monitoring of MRD show in peripheral blood a major molecular response (MMR) constant in time.

Meningeal relapse was confirmed in CSF by the presence of the BCR::ABL1B13A transcript with an imbalance score of 0.0002%.

Conclusions: Liquid biopsy (LB) of the cerebrospinal fluid has proven to be a very sensitive technique that allows the identification of molecular relapse on of free cell-free tumor DNA (ctDNA) in a less invasive way. The results of the molecular evaluation of the response to therapy by NGS study allowed the therapeutical switch to second generation TKIs Dasatinib.