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Acute Leukemias

ASSOCIATION OF ZAP-70 EXPRESSION AND CENTRAL NERVOUS SYSTEM (CNS) INFILTRATION AND RELAPSE IN ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Central nervous system (CNS) dissemination at diagnosis or during the course of the disease represents a primary unmet clinical need in the management of acute lymphoblastic leukemia (ALL), potentially more so in the immunotherapy era. *ZAP70* is a tyrosine kinase involved in T--lymphocytes maturation and activation, while *CXCR4* plays a role in the *CXCR4-CXCL12* axis, regulating hematopoietic stem cell homing in the bone marrow and lymph nodes. In *in vitro* studies, abnormal *ZAP70* and *CXCR4* expressions have been associated with CNS infiltration in ALL. Furthermore, a higher expression of *ZAP70* and *CXCR4* in bone marrow samples at diagnosis has been found in pediatric patients (pts) with B-ALL and T-ALL with a simultaneous CNS infiltration (Alsadeq A et al, Haematologica 2017).

Methods: *ZAP70* and *CXCR4* expressions were measured by reverse transcription quantitative polymerase chain reaction (RT-q-PCR; primers sequences are reported in Chiaretti S. et al,. Blood 2006). Expression levels of the genes were then correlated with clinical presentation and outcome to determine whether upregulation of these molecules was predictive of CNS infiltration and relapse.

Results: We assessed *ZAP70* and *CXCR4* expressions by RT-q-PCR in 85 diagnostic samples of adults with ALL: T-ALL, n=30, B-ALL, n=55, comprising 23 *BCR*::*ABL1*+, 16 *TCF3*::*PBX1*+, 2 *KMT2A*-r samples and 14 cases devoid of major molecular aberrations. In the preliminary analysis, we included only samples with >30% blasts (n=63) due to the known, and possibly confounding, expression of *ZAP-70* in T lymphocytes. *ZAP70* expression was heterogenous among individual cases. We next distinguished pts in CNS+ (either morphologic initial involvement or relapse, n=36, T-ALL=6) and CNS- (n=27, T-ALL=9): *ZAP70* expression in CNS+ was significantly higher than in CNS- cases (p=0.033). A subanalysis considering CNS relapses (n=18, T-ALL=3) alone versus CNS- pts (n= 27) also retained significantly higher levels of *ZAP70* expression (p<0.001). We also investigated the role of *CXCR4* in samples with >30% of bone marrow blasts. Unexpectedly, *CXCR4* expression did not show any differences between CNS+ and CNS- subgroups. To identify other potential markers of meningeal relapse, single cell RNA sequencing on a limited cohort of CNS+ vs CNS- pts (4 vs 6 samples) is ongoing (Cappelli LV et al, in preparation).

Conclusion. *ZAP70* expression in diagnostic bone marrow samples is associated not only with CNS infiltration at disease presentation but also with meningeal relapse in different subtypes of ALL, increasing the current knowledge on its role, previously limited to CNS infiltration at diagnosis.

Further analysis and validation will be performed on larger cohorts to confirm if *ZAP70* expression could be used as a predictive marker of CNS involvement in ALL with the incorporation of advanced tools and therefore might be useful to implement CNS-directed intensification.