Monitoring of childhood ALL using BCR-ABL1 genomic breakpoints identifies a subgroup with CML-like biology.

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Abstract

We used the genomic breakpoint between BCR and ABL1 genes for the DNA-based monitoring of minimal residual disease (MRD) in 48 patients with childhood acute lymphoblastic leukemia (ALL). Comparing the results with standard MRD monitoring based on immunoglobulin/T-cell receptor (Ig/TCR) gene rearrangements and with quantification of IKZF1 deletion, we observed very good correlation for the methods in a majority of patients; however, >20% of children (25% [8/32] with minor and 12.5% [1/8] with major-BCR-ABL1 variants in the consecutive cohorts) had significantly (>1 log) higher levels of BCR-ABL1 fusion than Ig/TCR rearrangements and/or IKZF1 deletion. We performed cell sorting of the diagnostic material and assessed the frequency of BCR-ABL1-positive cells in various
hematopoietic subpopulations; 12% to 83% of non-ALL B lymphocytes, T cells, and/or myeloid cells harbored the BCR-ABL1 fusion in patients with discrepant MRD results. The multilineage involvement of the BCR-ABL1-positive clone demonstrates that in some patients diagnosed with BCR-ABL1-positive ALL, a multipotent hematopoietic progenitor is affected by the BCR-ABL1 fusion. These patients have BCR-ABL1-positive clonal hematopoiesis resembling a chronic myeloid leukemia (CML)-like disease manifesting in "lymphoid blast crisis." The biological heterogeneity of BCR-ABL1-positive ALL may impact the patient outcomes and optimal treatment (early stem cell transplantation vs long-term administration of tyrosine-kinase inhibitors) as well as on MRD testing. Therefore, we recommend further investigations on CML-like BCR-ABL1-positive ALL.


http://www.bloodjournal.org/content/129/20/2771?sso-checked=true

Published: 8. 8. 2017 / Responsible person: Mgr. Ing. Tereza Kůstková

Source URL (modified on 28. 1. 2019 - 7:48):