Abstract

BCR-ABL1 fusion gene is a hallmark of chronic myeloid leukaemia (CML), but can be found also in patients with acute lymphoblastic leukaemia (ALL). In BCR-ABL1-positive ALL, two principal approaches for treatment response and minimal residual disease (MRD) monitoring are routinely used – quantification of genomic clonal rearrangements of immunoglobulin/T-cell receptor genes (Ig/TCR) and BCR-ABL1 expression. We established methods for determination of BCR-ABL1 genomic fusion and used the intronic breakpoints to measure MRD levels also at the BCR-ABL1 DNA level. Comparison of MRD based on Ig/TCR and genomic BCR-ABL1 in 47 consecutive childhood patients showed poor correlation in about 25 % cases with significantly higher BCR-ABL1 levels. In those patients, we found the BCR-ABL1 not only in ALL-blasts, but also in other cell subtypes (T-cells, myeloid cells) negative for clonal Ig/TCR rearrangements. For the similarity with CML we assigned this new leukaemia subtype with multilineage BCR-ABL1 involvement "CML-like" leukaemia. Our ongoing study is focused on the prognostic implications of discordant MRD results.

As we characterized the genomic BCR-ABL1 fusion in 428 patients (which is to our knowledge the largest cohort described so far), we also analysed the origin of the breakpoints. Our data suggest that non-homologous end joining seems to be the mechanism executing BCR and ABL1 fusion.

In contrary to the BCR-ABL1-pozitive ALL, childhood high hyperdiploid (HHD) ALL – defined by 51 to 67 chromosomes in malignant cells – have in general very good prognosis. However, some studies consider as HHD only patients with the DNA index (DNAi) ≥ 1.16, thus missing patients with lower ploidy and possibly worse prognosis. We investigated 89 HHD ALL patients with low-DNAi < 1.16 (LDi) and high-DNAi ≥ 1.16 (HDi). The HDi-HHD subgroup was enriched for (combined) trisomies with positive prognostic effect (particularly combined trisomy 4 and 18) and HDi-HHD patients were only rarely stratified to treatment group with high risk of relapse. Interestingly, expression analysis showed biological differences between HDi-HHD and LDi-HHD subgroups.

Our data both on BCR-ABL1 and on HHD subtypes provide new information on biology of childhood leukaemia with possible therapeutic and prognostic implications.