

Minimal residual disease in pediatric Acute Lymphoblastic Leukemia: BFM experience

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Acute lymphoblastic leukemia (ALL) in children has turned a mostly curable disease. However, 10-20% of children still suffer from a leukemia relapse. To optimize and economize treatment further, therapy must be tailored upon individual factors of relapse risk. Of these, one of the most relevant is response to treatment which can be estimated with high accuracy by assessing minimal residual disease (MRD) using either flow cytometry (FLOW) or molecular methods based on polymerase chain-reaction (PCR).

Since the early nineties, the Berlin-Frankfurt-Münster (BFM) study group – i.e. the primary association of clinical centers involved in leukemia treatment in Germany and Austria – developed, piloted, and applied MRD-diagnostics within four large-scale treatment trials. In study ALL-BFM 2000, PCR-MRD was used to stratify patients into three risk groups and turned out to be the most important, independent risk factor. During that trial, which was conducted in collaboration with the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), the collaborative AIEOP-BFM-FLOW study group, consisting of the four dedicated national reference centers (Berlin, Monza, Padova, and Vienna – M.N. Dworzak, coordinator), collected FLOW-MRD

data on more than 2000 patients, up to 11 samples per patient from 7 follow-up time-points, both blood and bone-marrow. Based on this huge amount of data we could prove that FLOW-quantification of MRD is a robust, standardizable assay which has additional and independent prognostic impact even when used in a multi-national, multi-centric treatment trial on top of using PCR-MRD for stratification. Most importantly, early response assessment by FLOW-MRD in bone marrow at day 15 of induction was found highly effective to discern a large cohort of patients with formidable outcome who could potentially profit from early treatment reduction. Based on these findings, FLOW-MRD is now incorporated as a tool to plan treatment intensity in the current ALL front-line trials AIEOP-BFM ALL 2009 and ALL IC-BFM 2009. These trials are conducted in 20 countries in- and outside Europe with an approximate combined annual accrual of 2000 patients. To organize and warrant standardized and quality assured FLOW-MRD diagnostics throughout the multinational consortium, the iBFM FLOW-group was founded and a twinning program between experienced and new centers established.