

## Minimal Disseminated Disease in Pediatric Non-Hodgkin Lymphoma

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In the pediatric lymphoblastic leukaemia the identification of individual malignant cells among normal bone marrow (BM) cells with highly sensitive assays provided, in the last 10 years, definitive proof that patients in complete clinical remission could be Minimal Residual Disease (MRD) positive and the clinical impact of these results are completely accepted by the scientific community [1].

For long time MRD was considered a biological parameter exclusively of haematological malignancies because BM involvement in solid tumor was considered an uncommon event. However in these last years, in pediatric Non-Hodgkin Lymphoma (NHL) different studies demonstrated that Minimal disease at diagnosis (MDD) could be a powerful tool for stratifying patients in different prognostic groups.

Burkitt's lymphoma (BL), Anaplastic Large Cell Lymphoma (ALCL) and Lymphoblastic T-cell lymphoma (T-LBL) are the three typical Non-Hodgkin Lymphoma of children, adolescents and young adults.

BL is characterized by t(8;14)(q24;q32) translocation accounting for about 75% of the total, which juxtaposes the c-myc gene to the immunoglobulin heavy chain (IGH@) locus on chromosome 14 in divergent orientation. LD-PCR and IgH rearrangement assay can be successfully used for MDD detection in these malignancies. The study of a large cohort of patients (134 BL specimens) showed that most of the molecular positive patients (85%) at diagnosis belonged to the R4 Risk Group (stage III or stage IV according to St. Jude staging classification and LDH>1000 U/l). The 3-year progression-free survival (PFS) was 68% ( $\pm 10\%$ ) in MDD positive R4 patients compared with 93% ( $\pm 5\%$ ) in MDD negative R4 patients ( $p=0.03$ ), whereas there was no difference in PFS between children with morphological BM involvement at diagnosis and those who had negative BM (PFS=67  $\pm$  14% vs. PFS=87  $\pm$  6%, respectively,  $p=0.12$ ) [2]. As a whole, results of MDD studies in BL may contribute to design better risk-adapted therapies, that may include novel anti-cancer drugs such as the anti-CD20 monoclonal antibody, in selected group of BL patients.

Anaplastic large cell lymphoma (ALCL) is frequently associated with the t(2;5)(p23;q35) chromosomal translocation, which gives rise to the fusion gene NPM-ALK. The fusion gene transcript can be readily and sensitively detected by PCR. Until some years ago, BM involvement was considered a rare event in ALCL, due to the subtle nature of the BM involvement and by the difficulty of its detection based on routine morphological examination. An international study performed in a large cohort of uniformly treated ALCL children demonstrated that MDD-positivity detected by PCR at diagnosis in BM or peripheral blood (PB) conferred a relapse risk of about 50%. In addition it's known that ALK over-expression may induce a host immune reaction, giving rise to autologous anti-ALK antibodies. The authors demonstrated that using MDD and antibody titer, patients could be divided into different biological risk groups with different prognosis. In particular progression-free survival (PFS) was only 28% for patients with low antibody titer and MDD-positive, compared to 93% for patients with high antibody titer and MDD-negative ( $P<0.0001$ ) [3]. In the current ALCL international protocol, taking into account only

clinical parameter such as mediastinal, visceral or skin involvement for risk stratification, the 3 yrs PFS was 58% for patients with clinical high-risk features vs 88% for standard risk patients. Thus the combination of MDD and antibody titer represents a new prognostic indicator that may be considered in the design of new ALCL trials.

Lymphoblastic T-cell lymphoma (T-LBL) and T-cell lymphoblastic leukemia (T-ALL) are often considered to be part of a spectrum of a single disease. The malignant cells in T-ALL and T-LBL are morphologically indistinguishable, and immunophenotype as well as genetic abnormalities of the cells are similar. The sensitive and specific methodologies used for MRD monitoring in T-ALL, such as PCR amplification of specific genetic abnormalities and clonal IG/TCR gene rearrangement, but also flow cytometric analysis can be used to detect sub-microscopic disseminated disease also in patients with T-LBL.

The very first data on the prognostic impact of minimal disease at diagnosis, evaluated by flow cytometry, was reported recently by Coustan-Smith et al. in 99 pediatric T-LBL patients [4]. Submicroscopic disease was detected in 72% of BM studied (71/99). In most of the patients a PB sample at diagnosis was also studied and every patient with detectable disease in the BM had also detectable disease in blood ( $r=0.86$ ,  $p<0.0001$ ). Using a cut-off level of 1%, the 2-year EFS was 68% for patients with higher levels of disease dissemination versus 91% for those with lower levels. These results indicate that flow-cytometric assay, that is at least 100-fold more sensitive than morphology, could allow a better stratification of patients for therapeutic purposes.

The overall scenario indicates that similar approaches used for MRD studies in ALL may be applied to analyze MDD-MRD in NHL patients. These studies are limited in solid tumors by the different nature of the primary disease compare to ALL, which implies availability of unfixed bioptic material.

Overall, risk stratification in future NHL clinical trials based on these newly identified risk categories should open up improved therapies enabling improved survival for high-risk patients while decrease toxicity for the low-risk patients.

### References

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