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Acute Leukemias

MINIMAL RESIDUAL DISEASE MONITORING IN PH+ ACUTE LYMPHOBLASTIC LEUKEMIA BY NEXT GENERATION SEQUENCING AND DIGITAL DROPLET PCR FOR IG/TR GENE REARRANGEMENT PRELIMINARY RESULTS FROM THE GIMEMA ALL2820 PROTOCOL

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Introduction: In Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL), BCR::ABL1 by quantitative reverse transcription polymerase chain reaction (RT-qPCR) is the gold standard for minimal residual disease (MRD) monitoring. The technique can however underestimate clonal complexity. Digital droplet PCR (ddPCR) and next generation sequencing (NGS) IG/TR analysis are alternative tools. This study aimed at evaluating: i) NGS versus standard PCR for IG/TR clonal marker screening; ii) the feasibility and clinical relevance of NGS-based MRD in a subset of patients and its concordance with ddPCR; iii) the correlation between molecular findings and clinical response.

Methods: Two hundred newly diagnosed adult Ph+ ALL patients enrolled in the frontline phase III GIMEMA ALL2820 trial - ponatinib + blinatumomab versus imatinib + chemotherapy - were investigated. Samples from both arms were collected at days +70 and +133. IG/TR clonality was assessed at diagnosis by PCR and by NGS (LymphoTrack IGH [FR1/2/3] and IGK). In few selected cases, NGS was performed to assess concordance with ddPCR.

Results: PCR and NGS provided a marker-positive result in 80% and 94.5% of cases, respectively; NGS recovery was 14.5%. By NGS, a total of 260 rearrangements were identified: 86% belonged to complete IGH recombination, while 14% involved IGK. On day +70, 110 patients were evaluated for MRD by IG/TR ddPCR. and On day +133 92 patients were evaluated In 40 patients, MRD was also assessed by NGS to evaluate the concordance with ddPCR, which was 87.5%. analysis on day +70 between evaluable patients who subsequently relapsed (8/110) vs those who did not (102/110) revealed that IG/TR by ddPCR was significant higher (p=0.001) in cases with disease recurrence. Likewise, on day +133, IG/TR values by ddPCR were significantly higher in relapsed patients (p=0.023). Finally , disease-free survival (DFS) was lower in IG/TR positive patients by ddPCR on both days +70 and +133 (p<0.001/ p<0.001) (Fig. 1).

Conclusions: In Ph+ ALL, NGS IG/TR marker screening allows to identify at diagnosis a greater number of clonal markers compared to PCR. The high concordance between ddPCR and NGS supports the reliability of NGS as a complementary tool for MRD evaluation, particularly in discordant/borderline cases. MRD assessment by ddPCR IG/TR seems to point to a strong correlation with relapse, as well as DFS.to highlight the sensitivity difference between two methods. The limited number of relapsed cases and the presence of 2 relapsed patients with a Ph-negative clone, suggest caution in reaching definitive conclusions. Comparison with BCR::ABL1 levels is ongoing.

Figure 1: Disease-Free Survival According to IG/TR Levels and ddPCR MRD