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The prognostic impact of clone-specific MRD in AML

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Recently, the understanding of the genomic landscape for Acute Myeloid Leukemia (AML) has led to the determination of clonal lesion profiles for patients at diagnosis. Studies using multi-target Minimal Residual Disease (MRD) strategies have revealed that molecular events clearance in Complete Remission (CR) is associated with improved prognosis in AML patients.

In order to evaluate whether a clone-specific MRD strategy can provide powerful prognostic information, Pierre Hirsch from the Sorbonne Universités, Centre De Recherche (CDR) Saint-Antoine, Paris, and colleagues used a multi-target strategy of Highly Sensitive-Next Generation Sequencing (HG-NGS) and chromosomal analyses to monitor MRD in the bone marrow and blood samples from sixty-nine AML patients. The results of the study were published ahead of print in Haematologica on 16th March 2017.

The key results of the study were:

- Median of 4 (range = 0–10) chromosomal or genetic events were identified per patient (68/69)
- Earliest clonal lesion was detected at high levels in First CR (CR1) samples from evaluable patients (30/65)
- Median Variant Cell Factor (VCF) of first lesion determined in CR1; 3.33%
- 2-year Leukemia Free Survival (LFS) in poor responders (VCF ≥ 3.33%; n = 26) and non-responders (VCF < 3.33%; n = 33); 31.7 ± 9.9% *vs* 51.7 ± 9.8%, *P* = 0.08
- 2-year LFS in responders (patients with 0 or 1 marker; n = 31) and non-responders (patients with 2 or more markers; n = 27); 64.9 ± 9.3% *vs* 19.8 ± 8.7%, *P* = 0.001
- 2-year Overall Survival (OS) in responders and non-responders; 84 ± 6.6% vs 57.1 ± 10.5%, *P* = 0.023
- Persistence of two or more lesions was an independent variable for OS (HR = 0.071, *P* = 0.006) and LFS (HR = 0.109, *P* = 0.0006)

In summary, the persistence of two or more lesions in CR1 is associated with poor prognosis and high risk of relapse in AML patients.

The authors concluded by highlighting that their study is feasible and shows the prognostic value of personalized clone-specific MRD evaluation that can be used in most patients with AML. Additionally, they suggested that large prospective studies should be carried out to evaluate if this strategy could be used to guide treatment decisions in AML patients.

Abstract

The genetic landscape of adult acute myeloid leukemias has been recently unraveled. However, due to their genetic heterogeneity, only a handful of markers are currently used for the evaluation of minimal residual disease. Recent studies using multi-target strategies indicate that detection of residual mutations in less than 5% of cells in complete remission is associated with a better survival. Here, in a series of 69 acute myeloid leukemias with known clonal architecture, we design a clone-specific strategy based on fluorescent in situ hybridization and high-sensitivity next generation sequencing to detect chromosomal aberrations and mutations, respectively, in follow-up samples. The combination of these techniques allows tracking chromosomal and genomic lesions down to 0.5-0.4% of the cell population in remission samples. By testing all lesions in follow-up samples from 65/69 evaluable patients, we find that initiating events often persist, and appear to be, alone, inappropriate markers to predict short term relapse. In contrast, the persistence of two or more lesions in more than 0.4% of the cells from remission samples is strongly associated with lower leukemia-free and overall survivals in univariate and multivariate analyses. Although larger prospective studies are needed to extend these results, our data show that a personalized, clone-specific, minimal residual disease follow-up strategy is feasible in the vast majority of acute myeloid leukemia cases.

References

1. Hirsch P. *et al*. Precision And Prognostic Value Of Clone-Specific Minimal Residual Disease In Acute Myeloid Leukemia. Haematologica. 2017 Mar 16. DOI: 3324/haematol.2016.159681. [Epub ahead of print].