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ISAL 2019 | The role of minimal residual disease guided treatment in acute myeloid leukemia

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On 26 February 2019, at the Acute Leukemias XVII Biology and Treatment Strategies biennial symposium in Munich, Germany, Professor Gert Ossenkoppele, chair of our Global Steering Committee, from the VU University Medical Center, Amsterdam, NL, discussed the role of minimal residual disease (MRD) guided treatment in acute myeloid leukemia (AML).[1]

Prognostic factors determined at diagnosis are predictive of outcome, and achievement of MRD complete remission (CR) during treatment may become an important end-point for survival. Professor Ossenkoppele illustrated that morphologic analysis is necessary for determining MRD but is also imprecise given the varied nature of CR status.[2] Therefore, the methods for determining MRD status need improving. Currently, two methods for detecting MRD status exist. These include:

- Quantitative polymerase chain reaction (qPCR)-based strategies which can detect translocations and mutations to a high level of sensitivity within two to five days
- Flow cytometry in which the leukemia-associated immunophenotype (LAIP) or 'difference from normal' techniques are utilized to a lower sensitivity level but over a shorter time-frame

The standardization of MRD assessment by Europe Against Cancer (EAC) concludes that the proportion of patients with AML informative for MRD detection utilizing qPCR is around 40%.[3] Professor Ossenkoppele explained the detection of MRD, based on the LAIP in patients with AML, which consists of the combination of primitive, myeloid, aberrancy-defining and pan-leukocyte markers. For example, in AML, the presence of an aberrant phenotype highlighted using the markers CD117 and CD2, can be used to mark the presence of leukemic cells at diagnosis and through the chemotherapeutic regimen, as well as identifying a phenotypically identical relapse. Moreover, flow cytometry analysis to detect MRD can be used in the post-transplant setting using the markers CD56 and CD13, which illustrates how MRD guided treatment can allow for remission following relapse.[4]

Professor Ossenkoppele highlighted the results from two prospective trials which showed that in patients who were MRD negative following chemotherapy, the incidence of relapse was lower compared to patients who were MRD positive at each stage tested, both in younger and older patients.[5,6] These studies highlighted that an MRD negative status prior to transplant was a significant determinant for improved overall survival (OS) and disease-free survival compared to patients who were MRD positive pre-transplant, raising the question whether transplantation is necessary. For patients with *NPM1* mutant AML, the most significant prognostic factor has been identified as molecular MRD status, with MRD positivity indicative of higher cumulative incidence rates of relapse and lower OS.[7]

Moreover, Professor Ossenkoppele illustrated that the trend in the literature suggests that for patients with MRD negative status, there is a greater estimated median survival time compared to patients with MRD positive status. The ELN 2017 guidelines included a new response category in patients with AML which outlined CR without minimal residual disease

(CR_{MRD-}).[8]

Professor Ossenkoppele discussed whether MRD guided therapy could benefit patients with AML, highlighting a benefit in high- and low-risk patients. Furthermore, in core-binding factor AML, a higher dosage of daunorubicin (90 mg/m^2/3 days) showed an improved clinical outcome with significantly lower levels of associated MRD compared to the standard dose (60 mg/m^2/3 days).[9] In addition to this, Professor Ossenkoppele discussed the results from the ALFA-0701 study (NCT00927498), highlighting the improvement in two-year OS and event-free survival in patients receiving gemtuzumab ozogamicin. In the HOVON-102 trial, Professor Ossenkoppele concluded that the MRD status correlated with outcome, and may be useful as an endpoint marker in drug development.

A major challenge is still present within the current diagnostic tools, with current methods to assess MRD proving insufficient. This is illustrated by the fact that approximately 30% of patients classified with low MRD levels still relapse, and 10–30% of patients with high MRD do not relapse. A leukemic stem cell (LSC) detection kit has been developed and this is able to identify the majority of $CD34^+CD38^-$ LSCs. The prognostic value of LSCs was demonstrated in the HOVON-102 study, which highlighted the lower cumulative incidence of relapse (CIR) and higher OS rates in patients with LSC negative status. Moreover, the HOVON-120 analysis illustrated that the combination of total blast MRD and LSC was a prognostic marker for outcome, with MRD^+LSC^+ patients demonstrating a higher CIR and lower OS. Professor Ossenkoppele concluded that for effective prognostication of patients, both LSC and MRD are critical.

A combination of technologies provides the enhanced opportunity to identify and classify patients according to disease status, with next-generation sequencing and flow cytometry both highlighting significant association with AML relapse.[10] Further to this, Professor Ossenkoppele discussed unpublished work with triple combination MRD techniques, highlighting that the utilization of combinations may allow for the detection of different subpopulations of leukemia cells.

To summarize, the ELN recommendations for MRD assessment include analysis pre-transplant and post-transplant, with clinical trials requiring further testing.[11] Professor Ossenkoppele concluded that MRD is present in AML; at present MRD directed therapy is not available but could become a clinical reality. Moreover, in all clinical trials, MRD should be assessed, with the value of MRD in terms of clinical outcomes requiring further investigation in randomized trials.

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