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Blood 142 (2023) 422–423

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Prognostic Role of Molecular MRD Variations during Treatment of Pediatric AML: A Retrospective AIEOP AML2013/01 Study

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Background. Measurable residual disease (MRD) is a key parameter to evaluate response to cytotoxic treatment in leukemia patients and, thus, to guide therapeutic strategies. In fact, the identification of persisting leukemia cells after chemotherapy is associated with an increased risk of disease recurrence, and many patients with acute myeloid leukemia (AML) experiencing relapse have a fatal outcome. Many somatic genetic aberrations are under investigation for assessing molecular quantitative MRD (qMRD). However, while flow cytometry is already recognized as useful in measuring residual disease levels, the impact of qMRD monitoring is still debated.

Methods and Results. We set up a qPCR assay to quantify mRNA fusion or mutated transcripts for 23 AML rearrangements identified at diagnosis in 247 patients (67% of the whole population) enrolled in our recently concluded AIEOP-AML2013/01 trial, with a sensitivity reaching $10^{-5/-6}$. We measured qMRD after the induction therapy courses (n=202) and identified 66 cases with qMRD>$1x10^{-3}$ (cut-off determined by ROC curve method, qMRD with respect to disease levels found at disease onset) and 136 with qMRD<$1x10^{-3}$ after the II induction course. Patients with qMRD>$1x10^{-3}$ had a significantly worse OS and EFS with respect to patients with qMRD<$1x10^{-3}$ (77% *vs* 89%, p=0.016 and 61% *vs* 78%, p=0.016, respectively). qMRD assessment within each AML risk group, namely Standard (SR, n=64), Intermediate (IR, n=38) or High (HR, n=101), showed that the persistence of qMRD>$1x10^{-3}$ after the II induction course in SR patients did not correlated with worse EFS with respect to patients who reduced qMRD levels below the cut-off, mainly due to *NPM1* mutated patients all relapsing (7/7) with qMRD<$1x10^{-3}$ after the second induction course. By contrast, qMRD>$1x10^{-3}$ was a predictive variable able to discriminate, among the patients assigned to the IR (EFS 46% *vs* 81% for IR, p=0.009) those children with poorer outcome. For the HR patients, qMRD $1x10^{-3}$ predicted a worse, although not statistically significant, outcome (61% *vs* 80% for HR, p=0.08).

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When we interrogated qMRD role within the different genetic subtypes, we showed that qMRD significantly impacted on EFS of patients harboring t(8;21) *RUNX1-RUNX1T1* (47% for qMRD>1x10 $^{-3}$ *vs* 88% for qMRD<1x10 $^{-3}$, p=0.004), this finding corroborating results previously published by our group. A similar trend, although not significant, was also obtained for patients harboring isolated *FLT3*-ITD mutation, who had a dismal EFS when qMRD levels after the II induction course were above 1x10 $^{-3}$ (40% (n=5) *vs* 71% (n=7) for qMRD<1x10 $^{-3}$, p=ns). qMRD reduction for *KMT2A*-rearranged AML cases and for other genetic markers having a lower incidence in AML, needs to be evaluated in larger cohorts to obtain robust results.
Additionally, we interrogated if qMRD maintains the same clinical relevance when measured after the III or IV chemotherapy blocks. We calculated proper cut-off for this analysis by ROC curve method, finding again 1x10 $^{-3}$ for the third chemotherapy cycle; we observed that AML cases with qMRD>1x10 $^{-3}$ had a worse EFS with respect to patients with lower levels of qMRD (39% n=30 *vs* 80% n=82, p<0.0001). As concerns the IV chemotherapy block, we calculated an appropriate cut-off corresponding to 1x10 $^{-4}$, and once again we confirmed that patients with qMRD above the cut-off displayed a lower probability of experiencing adverse events (EFS 49% n=46 *vs* 85% n=65, p=0.0003).
In conclusion, this is the first study that considers a serial and continuous qMRD monitoring all along an entire trial demonstrating a significant prognostic role of qMRD after II, III and IV therapy courses. These findings demonstrate that qMRD represents a useful tool in supporting therapeutic decisions and suggest that harmonization of currently used molecular MRD detection methods is the best solution to face MRD challenge in pediatric AML. Further comparisons between molecular and cytofluorimetric methods will increase the chances to identify those patients at high risk of relapse, despite negative MRD measured by flow cytometry.

Disclosures Merli: *Sobi:* Membership on an entity's Board of Directors or advisory committees; *Jazz:* Membership on an entity's Board of Directors or advisory committees; *Miltenyi:* Speakers Bureau; *Amgen:* Speakers Bureau. **Rizzari:** *CLINIGEN, JAZZ, SERVIER, SERB:* Consultancy, Honoraria, Speakers Bureau.

https://doi.org/10.1182/blood-2023-186918

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