The emerging role of MRD in AML

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Prognostic factors determined at diagnosis are predictive for outcome while achievement of morphological complete remission (CR) is still an important endpoint during treatment. Residual disease after therapy may reflect the sum of all diagnosis and post-diagnosis resistance mechanisms/factors, its measurement could hypothetically be very instrumental for guiding treatment. The possibility of defining residual disease (measurable residual disease: MRD) far below the level of 5% blast cells has changed the landscape of risk classification. Currently the two methods mostly used are flow cytometry based immune MRD (MPFC) and molecular MRD assessed by RT-qPCR. Both have advantages and disadvantages. MPFC can be applied in most cases of AML but is less sensitive than RT-qPCR which can however only be applied in 40% of cases. But new technologies are emerging like next generation sequencing and digital droplet PCR.

Although the concept of MRD negativity as an indicator for the quality of treatment response is the same in AML and other hematological diseases such as chronic myeloid leukemia (CML), multiple myeloma (MM), and acute lymphoblastic leukemia (ALL), application of MRD assessment in AML has lagged behind. Retrospective single center studies already demonstrated that MRD detection by MPFC provides strong prognostic information in AML after both induction and consolidation therapy. A couple of studies have now also been performed prospectively in a multicenter setting showing the independent prognostic value mainly determined after 2 cycles of chemotherapy. An example indicative for the usage of molecular MRD was recently published by Ivey et al who showed that the presence of MRD, assessed by q-PCR of NPM1 mutated transcripts, provided powerful prognostic information independent of other risk factors. Persistence of NPM1 mutated transcripts in blood was present in 15% of the patients after the second chemotherapy cycle and was associated with a greater risk of relapse after 3 years of follow-up than was an absence of such transcripts (82% vs. 30%; hazard ratio, 4.80) and a lower rate of survival (24% vs. 75%; hazard ratio, 4.38). Recently a meta-analysis of 81 publications reporting on 11,151 patients was performed. The average HR for achieving MRD negativity was 0.36 for OS and 0.37 for DFS. The estimated 5-year DFS was 64% for patients without MRD and 25% for those with MRD, and the estimated OS was 68% for patients without MRD and 34% for those with MRD. The association of MRD negativity with DFS and OS was significant for most subgroups.

Evidence is accumulating that the presence of MRD assessed by multi-color flow cytometry immediately prior to allogeneic HCT is a strong, independent predictor of post-transplant outcomes in AML. In a recent update, Araki et al. showed that in 359 adults, the 3-year relapse rate was 67% in MRD positive patients, compared to 22% in MRD negative patients, resulting in OS of 26% vs 73%, respectively. Depth of response prior to transplant, as measured by level of MRD, has emerged as one of the most important predictors of transplant outcome. Collectively, all these studies showed that low levels of MRD were associated with improved survival and lower risk of relapse superior to other well-defined prognostic factors such as AML type, age, WBC count at diagnosis, and classification of cytogenetic risk. Randomized trials are warranted to determine if MRD-guided preemptive therapy is associated with improved outcome. ELN published recommendation for the application of MRD. These will soon be updated.

Most available data are derived form studies with intensive treatment but now also more recent data show that also in non-intensive treated AML patients MRD has prognostic impact. MRD assessment in AML could be used 1) to provide an objective methodology to establish a deeper remission status, 2) to refine outcome prediction and inform post-remission treatment, 3) to
identify impending relapse and enable early intervention, 4) to allow more robust post-transplant surveillance, and 5) to use as a surrogate endpoint to accelerate drug testing and approval.

Various major AML trial groups now use MRD status to guide further treatment. The question whether MRD could be used as a surrogate endpoint for survival which would be very helpful for faster drug approval is still unsolved. It is important to recognize that MRD assessment should be part of every clinical trial in order to achieve this important goal.

New technologies evolve rapidly and will be discussed:
- next generation sequencing has been shown of prognostic value in clinical studies, although sensitivity is still low it is expected that this will change rapidly.\(^{10,11}\)
- assessment of the leukemic stem cell load is also prognostic for outcome.\(^{12}\)

Combinations of various methods are additive and increase the sensitivity: examples will be discussed\(^{10}\).

Literature
4a. Nicholas J. Short; Shouhao Zhou; Chenqi Fu; et al. JAMA Oncol. 2020;6(12):1890-1899.
7. Walter, R. B. et al. Comparison of minimal residual disease as outcome predictor for AML patients in first complete remission undergoing myeloablative or nonmyeloablative allogeneic hematopoietic cell transplantation. Leukemia 2015;29:137–44