Leukemia
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PERSPECTIVE

Acute myeloid leukemia

Should persons with acute myeloid leukemia (AML) in 1st histological complete remission who are measurable residual disease (MRD) test positive receive an allotransplant?

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> To him that hath, more shall be given; and from him that hath not, the little that he hath shall be taken away.
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> Mathew 25:29.

Increased understanding of the biology of acute myeloid leukemia (AML) has encouraged development of individualized therapy strategies, which focus on identifying which persons are likely to benefit from which interventions [1]. An example is using data from results of measurable residual disease (MRD) testing to predict outcomes and direct therapy [2]. Most data indicate persons with AML in histological complete remission with a negative MRD test have a markedly lower cumulative incidence of relapse (CIR) compared with persons with a positive MRD test [3–10]. This correlation led the European LeukemiaNet (ELN) to include histological complete remission with a negative MRD test as a new response category [11].

The question arises which persons with AML in 1st histological complete remission are appropriate candidates for an allogeneic haematopoietic cell transplant? The ELN AML working party consensus statement, using a dynamic risk-assessment approach including results of MRD testing, favors an allotransplant when the estimated leukemia relapse risk is >35–40% and when the projected improvement in disease-free survival (DFS) is >10% [12]. This is a complex calculus for several reasons some of which are insoluble. For example, estimating leukemia relapse risk at the subject-level even using data, such as results of cytogenetic testing and mutation analyses is imprecise with wide 95% confidence intervals. In many if not most instances these confidence intervals span the landmark point-estimates for leukemia relapse risk and DFS specified in the ELN recommendation. Many co-variates, often confounded, correlate with transplant outcomes such as age, co-morbidities, interval from remission to contemplated transplant, interval antileukemia therapy(ies), donor–recipient relationship and HLA matching, pretransplant conditioning regimen, posttransplant immune suppression. Also, the DFS endpoint does not account for persons with serious transplant-related complications such as chronic graft-versus-host disease (GvHD).

How might results of MRD testing be used to identify persons with AML in 1st histological complete remission are appropriate candidates for an allotransplant? Viewed simplistically and controlling for all other variables, known, unknown, and unknowable, transplants might be best used in persons with a positive rather than negative MRD test. This strategy assumes a transplant will overcome the high CIR associated with a positive MRD test. However, knowing this is true requires data from a randomized trial, in which persons who are MRD test positive are assigned to receive a transplant or not. There are no data from such a trial supporting this hypothesis. In contrast, data from some retrospective analyses, in which multi-parameter flow cytometry was used to test for MRD reported poor transplant outcomes in subjects who were MRD test positive pretransplant compared with those who were MRD-test-negative pretransplant [13]. This was so regardless of the intensity of pretransplant conditioning and donor–recipient type and HLA-matching. In one study, subjects in 1st histological complete remission who were MRD-test-positive pretransplant had a 3-year CIR of 67% like the 3-year CIR of 65% in subjects not in 1st histological complete remission (95% Confidence Intervals [CIs] not reported). Thol

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et al. [14] reported error-corrected next genome sequencing (NGS)-based MRD-testing pretransplant was highly correlated with CIR. The authors suggested NGS-based MRD testing might be useful to determine whether to give conventional or reduced-intensity pretransplant conditioning. Dillon et al. used reverse-transcription polymerase chain reaction to analyze pretransplant blood and bone marrow samples from 107 subjects with *NPM1* mutated AML [15]. Subjects were divided into three cohorts with no *NPM1* transcripts or low- or high transcripts. Two-year survivals were 83, 63, and 13% ($P < 0.0001$; CIs not reported). However, only the high transcript cohort had a worse CIR and survival when *FLT3* mutation was considered. A meta-analysis of 19 transplant studies reported a positive MRD-test pretransplant correlated with a higher CIR and worse leukemia-free survival (LFS) and survival, an impact independent of age, test used to detect MRD and pretransplant conditioning intensity [16].

Based on these extensive albeit imperfect data, some persons question whether an allotransplant is appropriate in persons MRD-test-positive pretransplant. This is, of course, exactly contrary to the hypothesis that persons at highest leukemia relapse risk are those most likely to benefit from a transplant. A retrospective analysis of 547 subjects enrolled in HOVON/SAKK studies reported that although subjects in all AML risk-categories defined by ELN 2017 classification benefitted from a transplant, absolute benefit was greatest in subjects who were MRD-test-positive pretransplant than in those who were MRD-test-negative pretransplant [17].

Leung et al. reported a correlation between MRD level detected pretransplant with CIR and survival in 58 children with AML in a retrospective analysis [18]. Buccisano et al. reported a similar correlation in 81 adults in another retrospective analysis [19]. No prospective study of this type is reported.

In a prospective multi-center study, Zhu et al. reported a MRD-directed risk stratification improved outcomes of 137 subjects with AML and a *RUNX1-RUNX1T1* mutation [20]. Subjects were tested for a *RUNX1-RUNX1T1* transcript after the 2nd consolidation course. Sixty-nine not achieving a >3 log-reduction in transcript levels were considered high risk for leukemia relapse, 49 of whom received a HLA-haplotype-matched allotransplant. The remaining 29 received more chemotherapy or an autotransplant. Allotransplant recipients had a significantly lower CIR and better DFS and survival compared with non-transplant subjects. However, assignment to an allotransplant was not random and there are obvious selection and *time-to-treatment* biases. In the GIMEMA AML1310 trial subjects who were intermediate risk and had a positive MRD test after consolidation therapy were to receive an allotransplant and those MRD test negative, an autotransplant. 2-year CIR, DFS, and survival were similar suggesting a transplant reversed the adverse prognoses of the MRD-test-positive cohort [21].

Hourigan et al. analyzed the impact of the intensity of the pretransplant conditioning on outcomes of subjects with AML in 1st histological complete remission randomized to receive conventional or reduced-intensity pretransplant conditioning retrospectively dividing subjects into two cohorts based on whether they were MRD-test-positive or -negative pretransplant using NGS testing [22]. Conventional and reduced-intensity conditioning regimens resulted in comparable 3-year CIRs and survivals in subjects who were MRD test negative. In contrast, in subjects who were MRD-test-positive 3-year CIRs were significantly higher and survivals significantly lower in subjects receiving reduced-intensity pretransplant conditioning (19% versus 67% ($P < 0.01$) and 61% versus 43% ($P = 0.02$; CIs not given). Although this study indicates better outcomes in subjects MRD test positive receiving conventional-intensity pretransplant conditioning it does not address the question whether outcomes of a transplant are better than conventional therapy in persons with AML in 1st histological remission who are MRD test positive.

Back to the question whether persons with AML in 1st histological complete remission who are MRD test positive should receive an allotransplant. The answer that can only come from a trial in which subjects who are MRD test positive are randomly assigned to an allotransplant or an alternative(s) such as placebo, additional anti-leukemia therapy, an autotransplant, an appropriate targeted therapy, or some combination such as in a so-called *basket trial*. Also, several outcomes need to be tested including, CIR, RFS, survival without GvHD, or relapse (GRFS), *quality-of-life* (QoL), and survival. Will such a trial be done? Unlikely. Even were it done analyses would need to consider prognostic features of the randomized cohort including type of MRD test used to assign positivity, sensitivity, specificity, rates of false-positives and -negatives in persons receiving chemotherapy-only, donor–recipient relationship and HLA-matching, pretransplant conditioning intensity, posttransplant immune suppression, and other co-variates.

And there are important limitations to what an MRD test can tell us. One limitation is measurement error. By reducing MRD-test results to positive or negative, we lose valuable quantitative data. Some subjects with a positive MRD test have many residual AML cells, others few. Then there are the important issues of sampling error and stochastic events [23, 24]. We discuss these and other limitations of MRD testing elsewhere [25].

We do not question the observation in persons with AML in 1st histological complete remission who are MRD-test-positive pretransplant have worse posttransplant outcomes compared with otherwise similar persons who are MRD-test-negative pretransplant. However, this observation has

nothing to do with our starting question: *Should persons who are MRD-test-positive pretransplant receive an allotransplant*. Is there a benefit for them receiving *versus* not receiving an allotransplant in CIR, LFS, GRFS, QoL, and/or survival? Put otherwise, should they be excluded from receiving an allotransplant simply because their outcomes are worse than persons who are MRD-test-negative pretransplant? Presently, there are no scientific bases for excluding persons who are MRD-test-positive pretransplant from receiving an allotransplant. They may benefit more than persons who are MRD test negative. Who knows?

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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