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TRANSPLANTATION

Comment on Murdock et al, page 3546

Transplant in older adults with AML: genomic wheat and chaff

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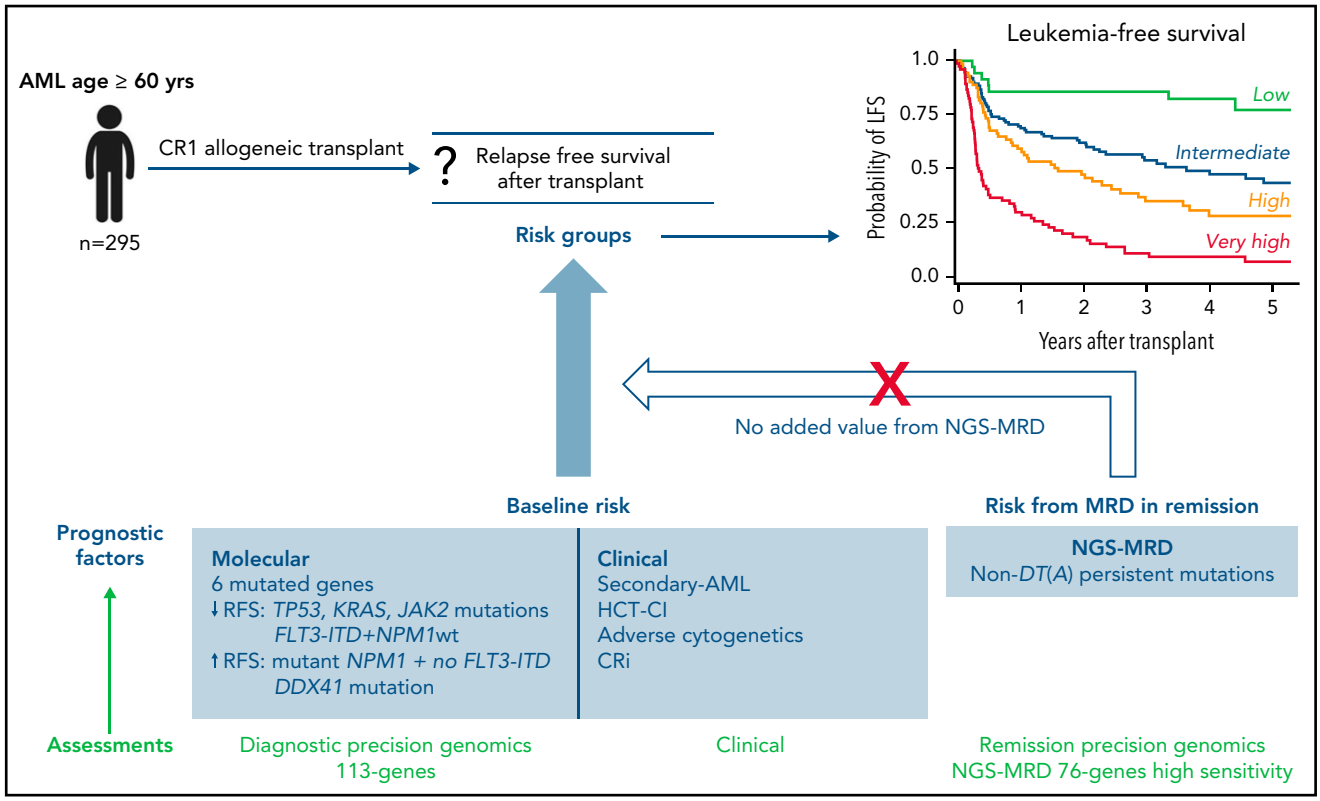
In this issue of *Blood*, Murdock et al[1] apply extensive diagnostic molecular profiling and measurable residual disease (MRD) detection of persistent mutations in a real-world cohort of older adults with acute myeloid leukemia (AML) to extract the most useful predictors of relapse-free survival (RFS) after allogeneic transplantation in first remission. Their results indicate that molecular persistence in remission is frequent in older adults and does not retain prognostic value for posttransplant outcomes after adjusting for specific baseline molecular and clinical variables.

Allogeneic transplantation provides the best chance for durable disease control for older adults with AML who have attained a first remission. Without a transplant, most will relapse within 2 to 3 years, even if they are among those with <0.1% residual leukemic cells by flow cytometry after 1 course of intensive chemotherapy.[2] Prompted by this finding, together with the advances in reduced-intensity conditioning (RIC) regimens and supportive care, many more patients with AML who are older than age 60 years are now routinely assessed as potential candidates for allogeneic transplantation.[3] Improving tools to inform the decision process for this age group is therefore a priority. Evaluating disease risk is of central importance because relapse is the major cause of transplantation failure.

In their study, Murdock et al first performed targeted next-generation sequencing (NGS) of 113 genes to profile mutations associated with myeloid malignancies in the diagnostic samples of 295 adults age 60 years or older, all of whom received a transplant during first remission (91% received RIC). From the 26 genes mutated in at least 3% of patients, only 6 were prognostic for RFS by univariable analysis, including *DDX41* mutations (present in 6%), which had a favorable impact on relapse. These genes, grouped into molecular risk tiers and then tested in a hierarchical risk model, independently influenced RFS as did certain known clinical risk factors (see figure). Not surprisingly, in line with other published data, the dominant molecular determinant of a high risk of relapse after transplantation was mutated *TP53*. The resulting poor RFS may be extrapolated to the older candidates for transplantation who presented with *TP53*-mutated myelodysplastic syndromes with excess blasts (MDS-EB) because outcomes and molecular characteristics do not differ between AML and MDS-EB when either one is *TP53* mutated.[4]

A clinical diagnosis of secondary AML also resulted in increased risk of relapse but not transplant-related mortality. Notably however, mutations associated with secondary genetic ontogeny, such as the splice factor and chromatin remodelling mutations, although frequent, were not prognostic in this transplantation cohort despite being associated with inferior outcomes in older adults after intensive chemotherapy.[5,6] This provides further evidence that patients in this AML genetic subgroup derive particular benefit from the combination of dose intensification delivered by a transplantation conditioning regimen and graft-versus-leukemia effect.[5] Conversely, clinical secondary AML (31% of patients) had increased therapeutic resistance to transplantation despite the predominant use of T-replete regimens. Whether this relates to clonal selection from previous nonintensive treatments such as hypomethylating agents or distinct leukemic characteristics is currently uncertain. However these results support proposals that alternatives to hypomethylating agents, including intensive chemotherapy, should be considered for fit adults with high-risk MDS or myeloproliferative neoplasm.

MRD results are increasingly considered in decisions regarding transplantation in patients with AML based on the independent prognostic impact of MRD across studies that include a range of MRD technologies, older adult cohorts, and randomized trials for transplantation.[7] However, data from NGS-based assays of AML MRD are predominantly from younger adults.[7] Murdoch et al sought to test the added value of NGS-measured MRD to their baseline molecular and clinical risk model for older adults who received a transplant. They extended their precision genomics to remission bone marrow samples, achieving an MRD level of sensitivity for a 76-gene panel by optimal reduction of technical background (error correction that included duplex unique molecular



Overview of findings from Murdock et al. Cohort heterogeneity (from variation in treatments, timing of MRD samples, and transplantation regimens) may be limiting factors for their prognostic model and therefore for its applicability to other groups of older patients with AML and specific first-line therapies. CR1, first complete remission; CRi, CR with incomplete recovery; HCT-CI, hematopoietic cell transplantation comorbidity index; ITD, internal tandem duplication; non-DT(A), mutations other than *DNMT3A*, *TET2*, and *ASXL1*; wt, wild type.

identifier tags). In all, 58% of patients had persistent mutations, even after excluding mutations in *DNMT3A*, *TET2*, and *ASXL1*, according to European LeukemiaNet (ELN) recommendations[7] based on NGS-MRD studies in younger adults; almost all were detected above a 0.1% variant allele frequency (ELN threshold for NGS-MRD positivity).[7] This molecular persistence was prognostic for RFS in univariable analysis, but it correlated with diagnostic genetic high-risk or secondary ontogeny characteristics, and crucially did not further discriminate outcomes predicted by the baseline risk model.

The findings of Murdock et al demonstrate that mutated genes with relative chemoresistance include many with indeterminate relapse-initiating potential in older adults, blunting the prognostic value of simply measuring persistent or emergent mutations for MRD. Similar to diagnostic genomic mutation panels, much mutation "chaff" must be filtered out to identify a useful prognostic MRD molecular signature in this setting. This will be challenging, especially with different clonal and subclonal sensitivities to evolving treatments and then transplantation. Experience points to the fact that older adults with residual preleukemic clones are frequently MRD negative by flow cytometry. We speculate that secondary-type AML mutation signatures with more oncogenic activity might correlate with blast aberrant immunophenotypes detected by flow cytometric MRD.

Another drawback for NGS-MRD is the loss of negative predictive value for known high-risk but often subclonal mutations in *FLT3* and other *RAS*-related genes. As supported by the study findings, these are less likely to be detected in remission; contributing factors may include detection limitations for more minor subclones, subclonal instability, or the effects of FLT3-targeted therapy.[8]

Given these results, NGS-MRD cannot currently be recommended as a standalone clinical assay in older patients with AML without more data to unravel the complexities. However, as an extension of diagnostic precision genomics, targeted NGS-MRD could feasibly be deployed when MRD relapse or progression is diagnosed by polymerase chain reaction (PCR) or flow cytometric MRD. This would allow clinicians to make early decisions regarding therapy, including peritransplant decisions, by determining whether actionable or high-risk mutations have been gained or lost from clonal evolution. This approach is being developed for the Australasian Leukaemia and Lymphoma Group INTERCEPT trial.

Although MRD negativity before transplantation predicts better outcomes, reduced intensity allografts can deliver MRD clearance early after conditioning and effective leukemic control for older adults with MRD-detected chemoresistance (or persistence) before transplantation.[9,10] Developing treatment pathways for the transplantation that minimize both selection of transplant-resistant clones and patient vulnerability to transplant toxicity is key in older patients with AML. This study provides significant advances to our understanding of treatment-related clonal dynamics in older patients with AML. It highlights that high-sensitivity genomics with standard MRD could be leveraged to distinguish transplantation-resistant MRD from chemotherapy-persistent MRD in treatment trials.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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