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# Do myelodysplasia-related gene mutations alter transplant decisions in *NPM1*-mutated acute myeloid leukemia? Comment on: "Prognostic implications of myelodysplasia-related gene mutations in *NPM1*-mutated acute myeloid leukemia: a systematic review and meta-analysis"

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# Do myelodysplasia-related gene mutations alter transplant decisions in *NPM1*-mutated acute myeloid leukemia? Comment on: "Prognostic implications of myelodysplasia-related gene mutations in *NPM1*-mutated acute myeloid leukemia: a systematic review and meta-analysis"

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To the Editor,

We read with interest the meta-analysis by Chang *et al*. evaluating the prognostic implications of myelodysplasia-related gene (MRG) mutations in *NPM1*-mutated acute myeloid leukemia (AML) (1). In this analysis, including 4,363 patients with *NPM1*-mutated AML, 655 patients (15%) harbored co-occurring MRG mutations. The presence of MRG mutations was associated with inferior overall survival (OS), [hazard ratio (HR), 1.30 (95% confidence interval [CI], 1.11-1.51; p<0.001)], shorter event-free survival (EFS) (HR 1.43; 95% CI, 1.11-1.85; p=0.006) and a lower likelihood of achieving complete remission (risk ratio 0.94; 95% CI, 0.90-0.99; p=0.01). On subgroup analysis, MRG mutations remained associated with inferior OS (HR 1.34; 95% CI, 1.14-1.59) within the ELN-2022 favorable-risk subgroup. These findings have important implications for risk stratification, but how they should inform transplant decisions requires careful interpretation.

In the European Leukemia Net (ELN) 2022 risk stratification, MRG mutations do not modify the favorable-risk designation conferred by *NPM1* mutation in the absence of *FLT3-ITD* or adverse-risk cytogenetics (2). Patients with *NPM1*-mutated AML who harbor MRG mutations but lack these additional high-risk features therefore remain classified as favorable risk and are not routinely referred for allogeneic hematopoietic cell transplantation (HCT) in first complete remission (CR1).

The data presented by Chang *et al.* raise an important clinical question: does a hazard ratio of 1.3 for OS justify reconsideration of HCT referral in CR1 for all patients with MRG mutations, or should decisions be individualized based on specific mutations and treatment response? In this meta-analysis, subgroup evaluation according to transplant status did not demonstrate a statistically significant survival difference attributable to HCT in CR1 (HR 1.46; 95% CI, 0.72-2.95 in transplanted patients; HR 1.09; 95% CI, 0.89-1.33 in non-transplanted patients; p=0.43), although these comparisons were limited by small numbers and potential selection bias. HCT

remains associated with non-relapse mortality, graft-versus-host disease (GVHD), and long-term morbidity. Whether the excess risk associated with MRG mutations is sufficient to warrant HCT in CR1 is not yet established.

The gene-level analyses in this study provide important nuance. Both this meta-analysis and recent large-scale European data demonstrate that *ASXL1* co-mutation confers substantially higher mortality (HR 2.27; 95% CI, 1.44-3.59), a magnitude approaching that reported for established adverse-risk categories (1,3). In contrast, *SRSF2* and *STAG2* were not significantly associated with inferior survival, aligning more closely with intermediate-risk outcomes. These findings suggest that aggregating biologically distinct MRG mutations into a single prognostic category may oversimplify clinical decision-making. In selected patients with NPM1-mutated AML and *ASXL1* co-mutation, individualized consideration of HCT in CR1 may be reasonable, though prospective data demonstrating survival benefit remain lacking.

The absence of patient-level MRD data is a critical limitation, as transplant decisions in contemporary practice are increasingly guided by molecular response rather than baseline genotype alone (4). Data suggest that achievement of deep molecular remission may mitigate adverse genomic signals, including those from MRG mutations (5). Given the risks associated with HCT, exposing MRD-negative patients to these harms without evidence of benefit is difficult to justify. In addition, the recent approval of menin inhibitors provides effective salvage therapy for relapsed *NPM1*-mutated AML, a consideration when weighing the risks of HCT in CR1 (6,7). Prospective studies integrating mutation-specific effects, MRD kinetics, and transplant-stratified outcomes are needed to determine whether HCT meaningfully improves survival in these patients. Until such data are available, HCT referral in NPM1-mutated AML with co-occurring MRG mutations should remain individualized, balancing genomic risk, treatment response, patient-specific factors, and transplant-related considerations.

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