

AML: Rethinking Intensive Therapy for Myelodysplasia-Related & Therapy-Related Subtypes

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Acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC) and therapy-related AML (t-AML) represent high-risk disease subsets with historically poor outcomes. Current guidelines often recommend intensive chemotherapy for eligible patients, but emerging data presented at EHA 2026 suggests a need to re-evaluate this approach, particularly concerning patient selection and the potential for alternative strategies.

KEY TAKEAWAYS

- **The Pivot:** Intensive chemotherapy may not offer a survival benefit for all patients with AML-MRC or t-AML, particularly those with adverse cytogenetics or poor performance status.
- **The Data:** Specific genetic markers (e.g., TP53 mutations, complex karyotype) are associated with significantly reduced response rates and overall survival following intensive therapy.
- **The Action:** Clinicians should consider a more nuanced risk stratification beyond age and general fitness when recommending intensive therapy for AML-MRC and t-AML, integrating molecular and cytogenetic profiles.

Acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC) and therapy-related AML (t-AML) are distinct entities characterized by a high incidence of adverse cytogenetics and molecular mutations, contributing to their aggressive clinical course and resistance to conventional chemotherapy.¹ Historically, intensive induction chemotherapy, typically with an anthracycline and cytarabine (7+3 regimen), has been the standard of care for younger, fitter patients.² However, the efficacy of this approach in AML-MRC and t-AML has been consistently lower than in de novo AML, prompting a re-evaluation of treatment paradigms.³ The EHA 2026 presentation focused on refining patient selection for intensive therapy, considering the inherent biological differences of these AML subtypes.

What the study did

The EHA 2026 presentation synthesized data from several large, prospective and retrospective cohorts of patients with newly diagnosed AML-MRC and t-AML, specifically examining outcomes following intensive induction chemotherapy. The analysis included patients from multiple international centers, totaling N=2,850 patients with AML-MRC and N=1,120 patients with t-AML. Eligibility for intensive therapy was based on standard criteria, including age generally under 70 years and adequate performance status (ECOG 0-2). The primary endpoints were complete remission (CR) rate, relapse-free survival (RFS), and overall survival (OS). Secondary endpoints included early mortality and incidence of treatment-related toxicities.⁴

A key aspect of the analysis involved detailed molecular and cytogenetic profiling for all included patients. This allowed for subgroup analyses based on specific genetic aberrations, such as mutations in TP53, FLT3-ITD, NPM1, and the presence of complex karyotypes or monosomal karyotypes. The study aimed to identify predictors of poor response to intensive therapy within these high-risk AML subsets.⁴

Key Findings

The pooled analysis demonstrated that while a subset of patients with AML-MRC and t-AML achieved complete remission with intensive chemotherapy, the overall response rates were significantly lower compared to de novo AML. For AML-MRC, the CR rate was 42% (95% CI, 40-44%), and for t-AML, it was 38% (95% CI, 35-41%). These rates contrast with typical CR rates of 60-80% in favorable and intermediate-risk de novo AML.⁵

Crucially, the study identified specific genetic markers that strongly correlated with poor outcomes following intensive therapy. Patients with TP53 mutations, present in approximately 20-30% of AML-MRC and t-AML cases, exhibited a CR rate of only 15% (95% CI, 12-18%) and a median OS of 6.5 months (95% CI, 5.8-7.2 months) after intensive chemotherapy. This was significantly worse than patients without TP53 mutations (median OS 14.2 months; $p < 0.001$).⁶ Similarly, patients with complex karyotypes (defined as ≥ 3 chromosomal abnormalities) had a CR rate of 28% (95% CI, 25-31%) and a median OS of 8.1 months (95% CI, 7.4-8.8 months), demonstrating a clear lack of benefit from intensive regimens.⁷

Early mortality (death within 30 or 60 days of induction) was also higher in these high-risk subgroups. For patients with TP53 mutations, 30-day mortality was 22%, compared to 10% in those without TP53 mutations ($p < 0.001$). This suggests that the toxicity of intensive therapy may outweigh its potential benefit in these particularly vulnerable populations.⁸

The analysis also explored the impact of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients who achieved CR. While allo-HSCT improved long-term outcomes for some, the high rates of primary induction failure and early relapse in the adverse-risk subgroups limited the number of patients who could proceed to transplant. For example, among TP53-mutated patients who achieved CR, the 2-year OS post-transplant was still only 30%, indicating persistent disease aggressiveness even after intensive consolidation.⁹

Limitations and Next Steps

The primary limitation of this pooled analysis is its retrospective nature for some cohorts, which can introduce selection bias. While molecular and cytogenetic data were comprehensive, heterogeneity in treatment protocols across different centers could also influence outcomes. Furthermore, the study did not directly compare intensive chemotherapy to less intensive regimens (e.g., hypomethylating agents with venetoclax) in a randomized fashion within these specific high-risk subgroups.¹⁰

Future research should focus on prospective, randomized trials comparing intensive chemotherapy with novel, less intensive combinations in AML-MRC and t-AML patients stratified by adverse genetic markers like TP53 mutations and complex karyotypes. The development of targeted therapies specifically for these high-risk subsets remains a critical unmet need. The data presented at EHA 2026 provides a strong rationale for moving beyond a 'one-size-fits-all' approach to intensive therapy in AML-MRC and t-AML.

CLINICAL IMPLICATIONS

The EHA 2026 data on AML-MRC and t-AML presents a clear challenge to the prevailing dogma of intensive chemotherapy for all eligible patients. For clinicians, the message is unambiguous: a patient's age and performance status alone are insufficient criteria for recommending intensive induction. The presence of adverse genetic markers, particularly TP53 mutations and complex karyotypes, should now prompt a serious reconsideration of the risk-benefit ratio. Continuing to offer a 7+3 regimen to a TP53-mutated patient, knowing their CR rate is 15% and early mortality is 22%, is difficult to justify when less toxic, potentially more effective alternatives are emerging, even if not yet universally approved for these specific indications.

This shift in understanding has significant implications for pharmaceutical companies. The market for novel agents in AML, especially those targeting high-risk subsets, is poised for growth. Companies developing drugs like magrolimab or specific TP53-targeting agents will find a more receptive clinical audience, as the limitations of conventional chemotherapy become starkly evident. The data underscores the need for more precision medicine in AML, moving away from broad-spectrum cytotoxic agents towards therapies tailored to specific molecular vulnerabilities. Guideline bodies, such as the NCCN and ELN, will need to rapidly integrate these findings to update their recommendations, ensuring that patient care reflects the most current evidence. For patients, this means a more personalized approach to treatment decisions. Instead of enduring the significant toxicities of intensive chemotherapy with minimal chance of benefit, patients with adverse genetic profiles may be offered alternative, potentially less burdensome, and more effective therapies. This could lead to improved quality of life and, in some cases, better survival outcomes by avoiding futile treatments. It also highlights the importance of comprehensive molecular testing at diagnosis, which should become standard practice to inform these critical treatment choices.

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