Therapy-Related Myeloid Neoplasms Following CAR-T Therapy: Emerging Patterns, Risk Factors, and Clinical Challenges

Safwan Muhammad, MD, Amna Shaukat, MD

Penn Medicine
Pennsylvania Hospital

INTRODUCTION

- CAR-T therapy has transformed outcomes in relapsed/refractory hematologic malignancies, expanding the population of long-term survivors.
- Therapy-related myeloid neoplasms (t-MN) include MDS, AML, MDS/AML and are an increasingly recognized late complication.
- Attribution to CAR-T is confounded by extensive prior cytotoxic chemotherapy and transplant exposure
- Emerging role for pre-existing clonal hematopoiesis (CH), TP53 abnormalities, and CAR-T-related hematopoietic stress
- Our study reviews incidence, risk factors, molecular features, and outcomes of t-MN after CAR-T.

METHODS

- Focused systematic review of studies reporting MDS/AML/t-MN after CAR-T, any product/target, any underlying malignancy.
- Prioritized primary cohorts with extractable incidence, risk factor, molecular, or outcome data.
- Excluded duplicate/overlapping cohorts, systematic reviews, isolated case reports from primary synthesis.
- 15 independent studies selected for qualitative synthesis after overlap assessment.
- Extracted: CAR-T product/target, malignancy, t-MN counts, MDS vs AML, time to onset, prior chemo/ASCT, cytopenias, CH/CHIP, cytogenetics, outcomes.

RESULTS

- Reported incidence ~2–6% across contemporary cohorts; up to ~9–10% with extended follow-up.
- Most t-MN cases arise within 1–2 years post-infusion, with later events reported.
- MDS more common than AML across cohorts.
- Heavily pretreated patients at highest risk (alkylators/bendamustine, platinum, melphalan, prior auto-SCT).
- Persistent post-CAR-T cytopenias frequently precede diagnosis.
- Older age, greater cumulative treatment burden associated with risk.
- Pre-existing CH increasingly identified in patients who later develop t-MN.
- Recurrent alterations: TP53, DNMT3A, RUNX1.
- Poor-risk/complex cytogenetics common.
- Pattern supports clonal selection/expansion of pre-existing clones over de novo leukemogenesis.
- t-MN reported after both CD19- and BCMA-directed CAR-T — not restricted to one target
- Associated with substantial morbidity, adverse cytogenetics, poor survival.

DISCUSSION

- Current evidence cannot clearly separate CAR-T's direct contribution from prior cytotoxic therapy and transplantation.
- Baseline CH/TP53-mutant clones may predate CAR-T; CAR-T-related hematopoietic stress may provide selective pressure for their expansion.
- Variability in incidence reflects differences in follow-up, patient selection, surveillance intensity, and competing mortality.

DISCUSSION

- Persistent cytopenias post-CAR-T should prompt bone marrow evaluation, especially in heavily pretreated patients.
- Prospective CH/mutation screening may improve risk stratification.
- Long-term hematologic surveillance increasingly warranted as survivorship extends.
- Limitations: Predominantly retrospective data, heterogeneous t-MN ascertainment, confounding from prior therapy/transplant, molecular data available in only a subset.

Conclusion

- t-MN is an uncommon but clinically serious complication of CAR-T therapy, with MDS predominating over AML
- Risk reflects prior therapy burden, transplant history, and pre-existing clonal hematopoiesis — CAR-T may select for vulnerable clones rather than directly cause disease
- Prospective molecular surveillance is needed to define true incidence and guide risk stratification

References

- Gazeau N, Beauvais D, Tilmont R, et al. Myeloid neoplasms after CD19-directed CAR T cells therapy in long-term B-cell lymphoma responders, a rising risk over time? Leukemia. 2025;39:1714-1722.
- Alkhateeb HB, Mohty R, Greipp P, et al. Therapy-related myeloid neoplasms following chimeric antigen receptor T-cell therapy for Non-Hodgkin Lymphoma. Blood Cancer J. 2022;12:113.
- Farina M, Bernardi S, Malagola M, et al. Real-world collection of secondary myeloid neoplasms after CD19 CAR-T cell therapy: first report of the ClonHema study. Bone Marrow Transplant. 2025;60:702-704.
- Tix T, Alhomoud M, Shouval R, et al. Second primary malignancies after CAR T-cell therapy: A systematic review and meta-analysis of 5,517 lymphoma and myeloma patients. Clin Cancer Res. 2024;30(20):4690-4700.