Risk of Therapy-Related Myeloid Neoplasms in Patients With Chronic Lymphocytic Leukemia Treated With BTK Inhibitors: A Retrospective Multicenter Analysis Using the TriNetX Database

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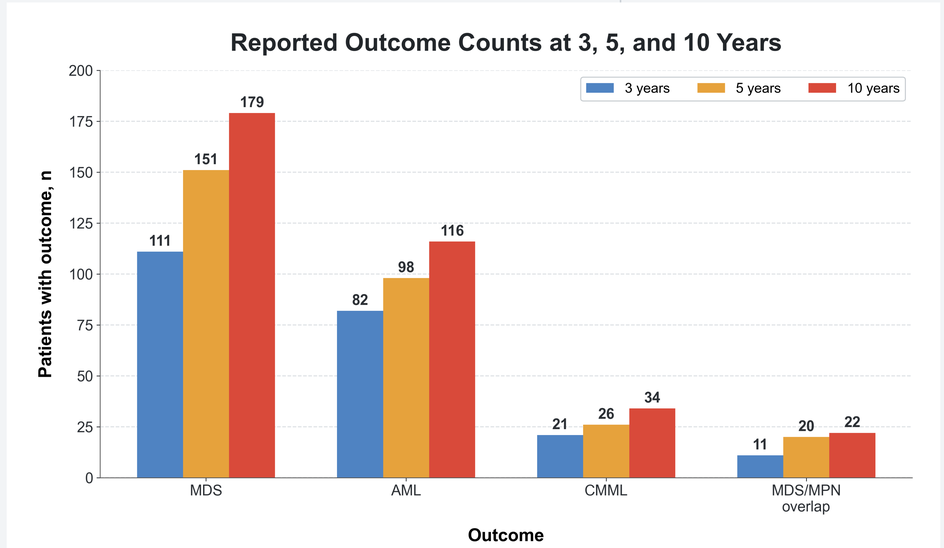
Background & objective

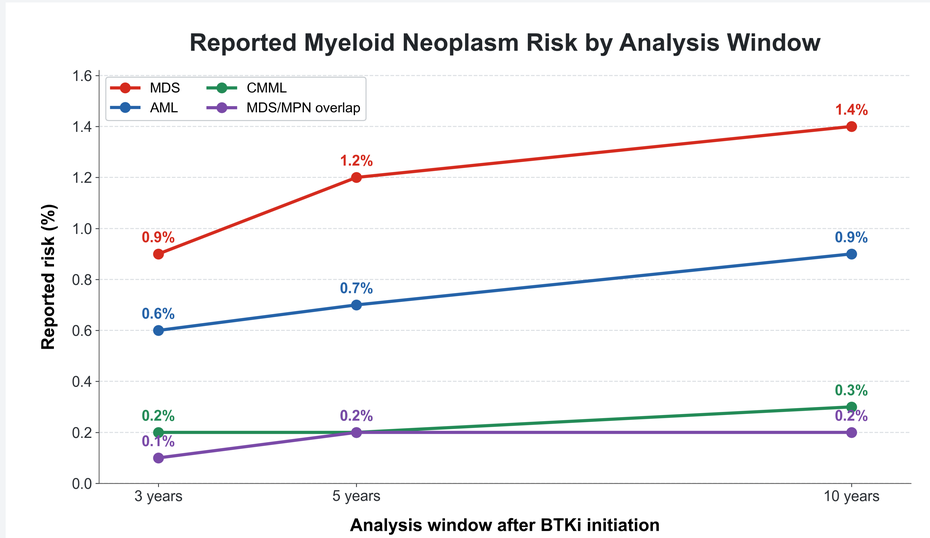
- Therapy-related myeloid neoplasms are important late complications of treatment for hematologic malignancies.
- The long-term risk after Bruton tyrosine kinase inhibitor (BTKi) therapy remains poorly characterized.
- **Objective:** Describe the proportions of patients with subsequent coded myeloid neoplasm diagnoses within 3-, 5-, and 10-year cumulative analysis windows after first BTKi exposure.

Methods

- **Design/source:** Retrospective cohort; TriNetX US Collaborative Network, 67 healthcare organizations.
- **Population:** Adults with CLL treated with ibrutinib, acalabrutinib, or zanubrutinib.
- **Exclusions:** Prior fludarabine/cyclophosphamide, FCR, bendamustine/rituximab, or obinutuzumab/chlorambucil.
- **Index date:** First BTKi exposure.
- **Outcomes:** New MDS, AML, CMML, or MDS/MPN overlap at 3, 5, and 10 years.
- Patients with an outcome before each analysis window were excluded.

Results





- We analyzed 13,234 adults with CLL treated with ibrutinib, acalabrutinib, or zanubrutinib.
- MDS was the most frequently recorded outcome, affecting 111 patients (0.9%) at 3 years, 151 (1.2%) at 5 years, and 179 (1.4%) at 10 years.
- MDS/MPN overlap was the least frequent outcome, occurring in 11 patients (0.1%) at 3 years, 20 (0.2%) at 5 years, and 22 (0.2%) at 10 years.

Conclusions

- Subsequent coded myeloid neoplasms were uncommon across all analysis windows among patients with CLL treated with BTK inhibitors.
- MDS was consistently the most frequent outcome, followed by AML, while CMML and MDS/MPN overlap remained comparatively rare.
- Longer cumulative windows captured more diagnoses, supporting continued longitudinal surveillance, although the retrospective design does not establish a causal relationship with BTK inhibitor therapy.

Interpretation & limitations

- This retrospective coded EHR analysis is subject to variable follow-up, incomplete ascertainment, coding errors, outcome-specific denominators, residual confounding, and the absence of an untreated or alternative-treatment comparator.
- The reported proportions do not account for censoring or competing mortality and should not be interpreted as fixed-horizon cumulative incidence or evidence of BTKi-related causality.

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