Targeted Therapy Era and Reclassification of Mantle Cell Lymphoma From Underlying to Contributing Cause of Death: 22-Year National Analysis

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INTRODUCTION

- Mantle cell lymphoma (MCL) has historically been an aggressive B-cell malignancy with short median survival, where lymphoma was almost universally the immediate cause of death.
- The introduction of Bruton tyrosine kinase (BTK) inhibitors (e.g., ibrutinib approved in late 2013) and contemporary targeted approaches has substantially improved disease control and survival duration.
- Whether prolonged survival is reshaping national death-certificate patterns toward a chronic contributing condition alongside competing non-malignant comorbidities remains uncharacterized.

AIM

- **Primary Aim:** Quantify national 22-year shifts (2003–2024) in the classification of MCL as the underlying cause of death (UCOD) versus a contributing multiple-cause-only (MCOD-only) condition.
- **Secondary Aim:** Evaluate trajectory inflection points across pre-targeted (2003–2013) and targeted therapy (2014–2024) eras and identify non-MCL causes replacing lymphoma mortality.

METHOD

Data Source: CDC WONDER / NCHS Multiple Cause of Death records (2003–2024) evaluating decedents with MCL (ICD-10 code C83.1) in underlying or contributing entity fields.

Outcomes: Proportion of MCL-associated deaths classified as MCL-as-UCOD vs. MCOD-only; distribution of competing non-MCL UCODs (cardiovascular, second malignancies, respiratory, infections).

Statistical Analysis: Binomial logistic regression and piecewise regression with an inflection knot at 2013 comparing pre-targeted vs. modern targeted eras.

CONCLUSIONS

Real-world national mortality data demonstrate a significant reclassification of MCL from the **direct driver of death** toward a chronic **contributing** disease phenotype.

The accelerated decline in MCL-as-UCOD classification after 2013 highlights how targeted agents have prolonged disease control, emphasizing the growing clinical need for long-term comorbidity mitigation, infection vigilance, and survivorship-focused care in MCL.

RESULTS

National Cohort (N=25,060): Identified 9,061 MCL-associated decedents in 2003–2013 and 15,999 in 2014–2024.

Decline in MCL as Underlying Cause: Proportion of deaths with MCL as UCOD fell from **88.6%** (pre-2014) to **81.1%** (modern era), while contributing-only mentions rose from **11.4% to 18.9%**.

Inflection Post-2013: Piecewise regression showed a flat pre-2013 trend (OR 0.996, p=0.649) with a significant post-2013 acceleration in UCOD decline (slope-change OR **0.922**, 95% CI 0.900–0.945, p < 0.001).

Shifting Mortality Ratio & Competing Causes: The ratio of MCL underlying to contributing deaths dropped from **7.74 to 4.30** across eras, while non-malignant UCODs nearly doubled (**6.6% to 12.7%**).

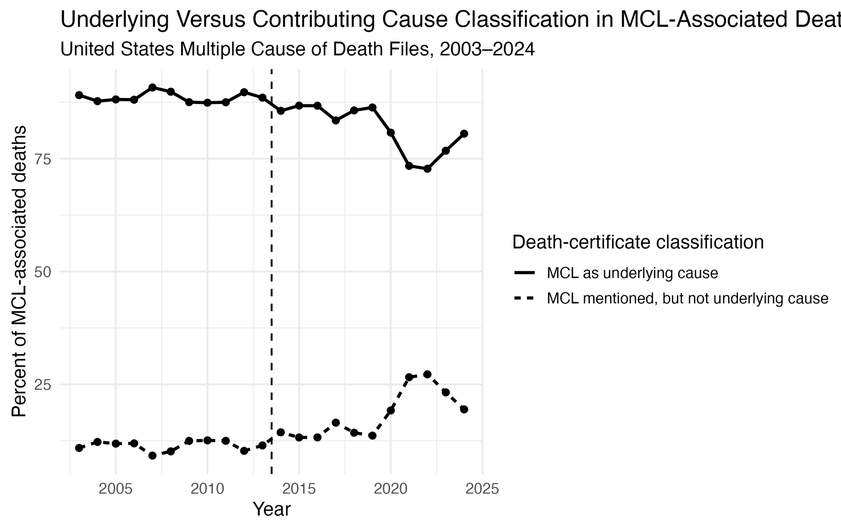

Figure 1. 22-Year Divergence in Underlying Versus Contributing Mortality Classification in Mantle Cell Lymphoma (2003–2024). Annual proportions of nationwide MCL-associated decedents listing MCL as the primary underlying cause of death (solid line) versus a contributing condition (dashed line). The dotted vertical line denotes the 2013 inflection knot (FDA approval of ibrutinib). In the targeted therapy era, MCL is increasingly recorded as a contributing chronic condition rather than the sole immediate cause of death.

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