Patients with high-risk features in mantle cell lymphoma: A systematic literature review of clinical trials and real-world studies

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ABSTRACT

Introduction

Given the low incidence of high-risk mantle cell lymphoma (MCL), conducting a systematic review and pooling data across studies are important potential methods for establishing a benchmark for outcomes with standard of care therapies for these patients. Limited studies have systematically examined patient (pt) characteristics and outcomes associated with high-risk MCL. This study aims to systematically review and comprehensively synthesize published evidence from randomized clinical trials (RCTs) and real-world data (RWD) to evaluate outcomes among patients with and without high-risk MCL in the era emerging novel therapies.

Methods

A systematic literature review (SLR) was conducted using Embase, PubMed, and CENTRAL (Jan 2020 - Apr 2025) to identify RCTs and RWD studies in the treatment-naïve (TN), relapsed/refractory (R/R), and/or post-Bruton tyrosine inhibitor (BTKi) MCL settings. Studies evaluating the impact of high-risk and non-high-risk features on overall response rate (ORR), complete response (CR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), time to next treatment (TTNT), adherence, healthcare resource utilization (HCRU), healthcare costs, and health-related quality of life (HRQoL) in the TN, R/R, and/or post-BTKi MCL settings were included. High-risk features included *TP53* mutation, Ki-67 index, Mantle Cell Lymphoma International Prognostic Index (MIPI) score, blastoid or pleomorphic morphology, and complex karyotype (≥3 abnormalities). Unadjusted pooled analyses (sample size allowed) were performed for RCTs and RWD studies separately to descriptively summarize ORR and CR rates by high-risk features and treatment settings. Weighted and median PFS/OS and DOR were also reported when sample sizes were adequate.

Results

This SLR identified 133 unique studies across TN, R/R, and post-BTKi MCL settings; only 39 were included due to the reporting of outcomes for high-risk features (12, 14, and 4 RCTs; 7, 7, and 1 RWD studies, respectively). *TP53*, MIPI, Ki-67, and morphology were the most commonly assessed high-risk features. Complex karyotype was infrequently assessed and therefore not summarized in this review. ORR, CR, OS, and PFS were commonly reported, while data on DOR, HRQoL, and RW outcomes by risk status were limited.

In CTs, pts with *TP53* mutations had lower pooled ORR vs unmutated pts across TN (91.1% vs 95.3%), R/R (70.9% vs 86.8%), and post-BTKi (73.8% vs 85.2%) settings. CR rates were also lower in *TP53*-mutated pts in TN (68.9% vs 85.0%), R/R (57.4% vs 79.4%), and post-BTKi (68.0% vs 77.4%). In R/R RCTs, weighted 1-year PFS (41.3% vs 68.1%) and OS (65.9% vs 80.2%) were lower in *TP53*-mutated pts. These findings were consistent with TN RWD studies, where median PFS was 6.7–11.4 months (m) for *TP53*-mutated pts vs 21.6–24.2 m for unmutated; median OS ranged from 11.3–99.6 m vs 21.6–170.4 m, respectively.

In R/R MCL RCTs, pts with high-risk MIPI had a lower pooled ORR (65.3%) vs pts with low/intermediate MIPI (82.4%). In RW studies, weighted 3- and 5-year OS were lowest in high-risk MIPI pts (56.0% and 36.6%), followed by intermediate-risk (73.3% and 55.7%), and highest in low-risk pts (85.9% and 74.1%). In RCTs of TN pts, pooled ORR and CR were similar between Ki-67 ≥30% (98.7%, 84.0%) and <30% (98.3%, 85.7%). In R/R RCTs, ORR was lower for Ki-67 ≥30% (77.7%) vs <30% (88.7%), while CR was lower for Ki-67 ≥30% (71.0%) vs <30% (82.3%). In RW studies of TN pts, the weighted 5-year OS was lower for pts with Ki-67 ≥30% (55.6%) compared to pts with Ki-67 <30% (71.1%).

In comparing outcomes in blastoid/pleomorphic vs classical MCL, CTs showed similar pooled ORR in TN (98.1% vs 100%) and in R/R (80.1% vs 81.9%) and lower ORR in post-BTKi (71.2% vs 76.0%) settings. Blastoid/pleomorphic MCL had similar CR rates in TN (87.0 % vs 87.2%) and lower CR rates in R/R (59.7% vs 76.5%) and post-BTKi (59.1% vs 74.1%) settings compared to classical MCL. RW data on outcomes by morphology is limited.

Conclusions

This SLR reinforces the existing unmet need in pts with high-risk MCL. Across both RCTs and RWD settings, pts with high-risk MCL including *TP53* mutations, high-risk MIPI, and Ki-67 >30% consistently experienced worse outcomes vs lower-risk pts. These findings highlight the disease burden and unmet need for better treatments in MCL pts with high-risk features. Further RCT and RWD studies are needed to better understand impact of high-risk features on long-term outcomes.