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CMV in the Shadows of Bendamustine–Rituximab Therapy: A Meta-analytic Insight

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Bendamustine, an alkylating agent, and rituximab, an anti-CD20 monoclonal antibody, are frequently used together (Bendamustine--Rituximab [B-R] regimen) to treat indolent lymphomas. While this regimen is more efficacious than older protocols, it is also associated with significant immunosuppression; bendamustine causes lymphopenia, and rituximab leads to hypogammaglobulinemia.[1] Emerging reports suggest an increased risk of cytomegalovirus (CMV) reactivation in this setting.[1]

We conducted a systematic review and meta-analysis to estimate the incidence of CMV reactivation, defined as either infection (viremia/antigenemia) or disease (organ involvement), in patients receiving B-R. The study followed PRISMA guidelines and was registered with PROSPERO (CRD42024557187). A systematic search of PubMed and Embase was conducted through March 26, 2024, using the following strategy: (lymphoma OR leukaemia OR leukemia) AND (bendamustine) AND (rituximab) AND (CMV OR HCMV OR cytomegal*). Studies were screened independently by two authors (P.K.T. and A.S.) and discrepancies were resolved by a third author (N.G.). They were included if they reported CMV reactivation in indolent lymphoma patients treated specifically with B-R, without other agents. Studies of aggressive lymphomas or monotherapy were excluded.

Twelve studies met the inclusion criteria out of 261 initially screened articles (►**Supplementary Fig. S1**, available in the online version only). All included studies fulfilled more than five of the eight items on the JBI checklist for prevalence studies (►**Supplementary Table S1**, available in the online version only). Due to the small number of studies, funnel plot analysis was not performed. Individual patient data ($n = 14$) from eight studies were reviewed. B-R was used primarily for follicular (50%) and mantle cell lymphoma (42.8%) (►**Supplementary Table S2**, available in the online version only). CMV disease developed after a mean of 3.8 ± 1.7 cycles and involved the gastrointestinal tract ($n = 7$), eyes ($n = 5$), liver ($n = 5$), and lungs ($n = 2$). The median lymphocyte count at onset was 120/µL (range 74–561), and the clinical recovery rate was 64.2% (9/14).

Six observational studies contributed to the pooled incidence estimates (►**Supplementary Table S3**, available in the online version only). CMV infection or disease rates ranged from 2.4 to 30.3%. Using a random-effects model (DerSimonian and Laird), the pooled incidence of CMV infection was 7.1% (95% CI: 2.5–11.8%), with significant heterogeneity ($I^2 = 73.1\%$). CMV disease incidence ranged from 2.6 to 7.4% (►**Fig. 1**).

CMV is a herpesvirus that remains latent after initial infection and employs multiple immune evasion strategies.[2]

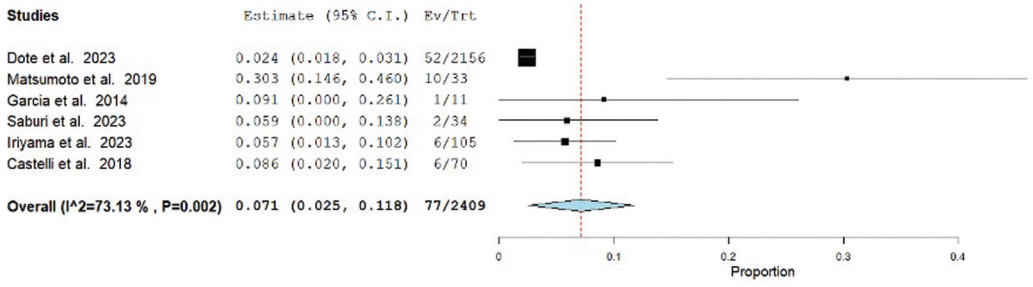

Fig. 1 Random effects meta-analysis of the incidence of CMV infection in patients with indolent lymphomas receiving bendamustine–rituximab regimen. CMV, cytomegalovirus.

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In immunosuppressed hosts, including chemotherapy recipients, CMV can reactivate, causing systemic or localized organ disease. Although its impact is well-documented in transplant settings, where routine prophylaxis is standard,[3] CMV reactivation in lymphoma patients is less well studied. In addition to direct cytopathic effects, CMV reactivation may impair immune function, increasing susceptibility to other infections and contributing to poor outcomes, even in the absence of clinically overt disease.[3] Detection may be underestimated due to a lack of screening; for instance, Matsumoto et al reported higher rates with routine antigenemia monitoring.[4]

Given CMV's tropism for vital organs and associated morbidity, our findings support routine consideration of surveillance or prophylaxis in high-risk patients. Limitations include the small sample size, heterogeneity, and absence of comparator regimens. Nonetheless, CMV reactivation is a clinically significant, underrecognized complication in B-R-treated lymphoma patients.

Authors' Contributions

P.K.T. and N.G. were involved in the conception and design. P.K.T., S.R.N., and A.S. were involved in data acquisition, analysis, and interpretation. N.G. and P.K.T. were involved in the critical review. All authors read and approved the final manuscript.

Data Availability Statement

Any additional data can be requested at a reasonable request by the corresponding author.

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