

(PS2411) INTEGRATIVE BIOINFORMATIC AND REAL-WORLD DATA ANALYSIS REVEAL MECHANISTIC ASSOCIATIONS BETWEEN LETERMOVIR PROPHYLAXIS AND EBV REACTIVATION AFTER ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Topic: 31. Infections in hematology (incl. supportive care/therapy)

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Background

Letermovir, a cytomegalovirus (CMV)-specific terminase inhibitor, has become an essential prophylactic agent in allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, our previous research and other evidences have linked its use to increased Epstein-Barr virus (EBV) reactivation.

Aims

We aim to investigate the mechanisms underlying the association between letermovir treatment and EBV reactivation.

Methods

We integrated pharmacoinformatics, transcriptomic validation, and real-world clinical data to investigate letermovir-EBV associations. EBV- and letermovir-associated targets were mined from public databases, with overlapping targets analyzed for hub protein identification. Molecular docking assessed letermovir binding affinities, and GO/KEGG/Reactome enrichment identified key pathways. Gene expression of overlapping and hub targets was validated using GEO datasets modeling EBV reactivation. Clinical data from 276 haploidentical HSCT recipients (145 received letermovir prophylaxis, 131 without) were analyzed for EBV-associated outcomes, with Cox regression used to construct a prediction model.

Results

Fifty-eight overlapping targets were identified. Hub proteins included EGFR, ERBB2, HIF1A, PPARG, PTGS2 and STAT3, with molecular docking indicating stable binding to letermovir. Enrichment analysis identified hypoxia response, immune/inflammatory, and endothelial/angiogenic pathways. GEO datasets confirmed stage-specific expression of overlapping and hub gene during EBV reactivation. Clinically, patients receiving letermovir prophylaxis after HSCT had higher EBV viraemia, EBV infection and clinically significant EBV infection rates. Risk factors for EBV infection included early elevation of thrombin-antithrombin complex (TAT), D-dimer, and pro-inflammatory cytokines among LTV group patients, different from those without letermovir. A prediction model demonstrated good performance and clinical utility, stratifying patients into high- and low-risk groups with significantly different EBV infection.

Summary/Conclusion

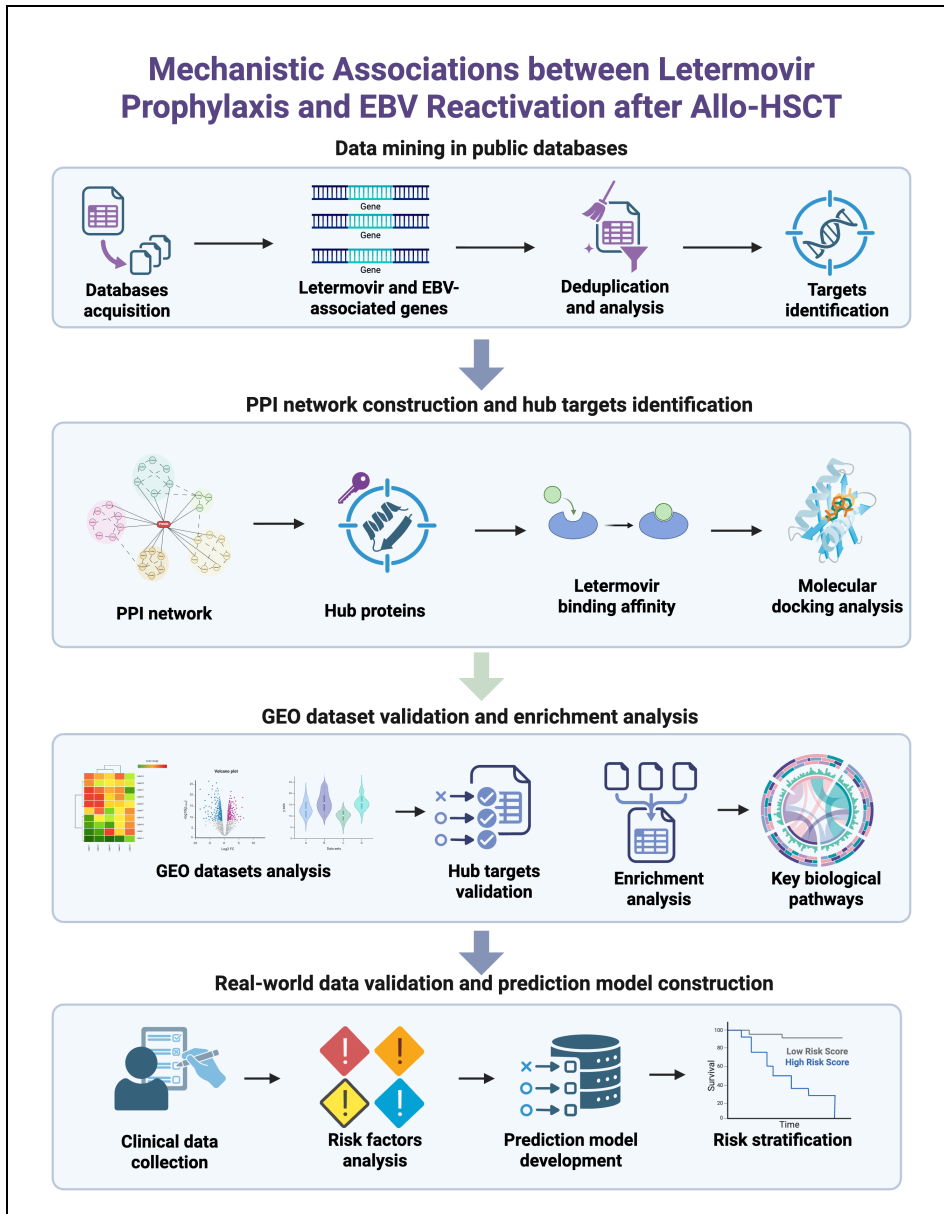
The use of letermovir for prophylaxis may contribute to a higher risk of EBV reactivation post allo-HSCT by disrupting key biological pathways involved in hypoxia, inflammation, and endothelial function. Our integrative model facilitates early identification of patients at high risk of EBV reactivation, guiding monitoring and intervention strategies.

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Flowchart of the study

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