Persistent Epstein-Barr virus viremia in NK-/T-cell lymphoma: bad boys for life!

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Received: May 8, 2025.
Accepted: May 20, 2025.
Early view: June 5, 2025.

https://doi.org/10.3324/haematol.2025.287922

In this issue of *Haematologica*, Zhong *et al.*[1] report the long-term outcomes of a large, open-label randomized phase III trial that included patients aged 14-70 years with early-stage natural killer cell (NK) / T-cell lymphoma (NK-TCL) treated with either etoposide, dexamethasone, and pegaspargase (ESA) or methotrexate + ESA (MESA) combined with sandwiched radiation therapy. There was non-superiority in efficacy between the two chemotherapy regimens. Importantly, this study evaluated pre-treatment, interim, and post-treatment plasma Epstein-Barr virus (EBV) DNA levels in correlation with treatment response, as well as other changes in the tumor microenvironment (TME).

Natural killer cell / T-cell lymphoma is an EBV-driven hematologic malignancy that occurs predominantly in patients of Asian descent. The striking association suggests, in part, a complex interaction of viral exposure, genetic and/or environmental factors in NK cell / T-cell lymphomagenesis. The authors should be congratulated for providing valuable information on the correlation of persistent EBV viremia detection and inferior clinical outcomes. These findings suggest that EBV may, in part, regulate the NK/T lymphoma TME and influence the response to therapy, and demonstrates that plasma EBV levels would serve as an important surrogate biomarker for treatment response and outcomes in early stage NKTCL patients.

The characteristic ability to remain latent in memory B cells and to reactivate (lytic replication) under host immunodeficiencies is linked to EBV tumorigenesis in a broad-spectrum of B-cell malignancies.[2] For instance, EBV positivity in Burkitt lymphoma (BL) is associated with a distinct molecular profile and activation of specific signal transduction pathways (overexpression of proteins linked to lymphomagenesis) in comparison to EBV$^-$ BL and are presumably linked to EBV only, and independently of age, geographic region, or host immune status.[3-5]

The association between EBV and NK-cell /T-cell malignant transformation is less well understood. Integration of the virus into NK / T cells occurs while trying to eliminate EBV infected cells. There is propagation of the viral genome either in episomal and/or fully integrated forms into the host genome (EBV isolates cluster according to their geographic origin).[6] In NKTCL, multiple EBV genome insertions/deletions, and EBV-host integration sites are found, leading to NKTCL specific mutations (*BPLF1*, *EBNA* family) or mutations found in other EBV-driven neoplasms, like in *EBNA1*, *EBNA3*, and *LMP1*. Interestingly, a large number of T-cell non-synonymous epitope alterations are found in NKTCL, supporting an additional mechanism of immune evasion by NKTCL cells.[6]

It has been postulated that activation of specific EBV genes (such as *LMP1*) leads to additional genetic alterations in this disease. For instance, abnormalities involving chromosome 6 are common, in addition to recurrent mutations involving JAK-STAT or RAS-MAPK signaling pathways, RNA helicase family, apoptosis, and epigenetic modifiers genes. Epigenetic alteration such as hypermethylation of cell cycle regulators, tumor suppressors and histone modification have been found. Additionally, EBV latent viral proteins lead to overexpression of genes involved in an increase in cell proliferation, decreased apoptosis, immune evasion, and resistance to therapy.[1,7]

However, it seems that not only features intrinsic to the tumor are linked to tumor survival and response to conventional chemotherapy. A host-specific characteristic represented by the detection of EBV in the plasma is also linked to treatment response and outcomes. It has been well established that plasma EBV detection/titer levels measured by polymerase chain reaction are associated with NKTCL disease activity, dissemination, and response to therapy.[6,7] In the manuscript by Zhong *et al.*,[1] the authors provide additional insights into the cellular processes likely triggered by the circulating EBV and the dynamic changes in viremia levels during NKTCL treatment.

Importantly, in their cohort, about half of the patients had

detectable EBV viremia prior to initiation of chemotherapy. They compared clinical characteristics, immunohistochemistry, and RNA-sequencing results between the 2 treatment groups. Analysis of functional pathways showed that patients with EBV$^+$ viremia were found to have significant enrichment in neutrophil extracellular trap formation, ATP-dependent chromatin remodeling, viral carcinogenesis, metabolism, and nucleocytoplasmic transport. In patients with EBV$^-$ viremia, they found enrichment of immune-related pathways, IL-17 signaling, and PPAR signaling (Figure 1). Intriguingly, the authors demonstrated different gene expression profiles from patients with positive *versus* negative EBV detectable viremia at interim analysis. Patients' tumor samples at diagnosis from those who sustained interim EBV viremia had a diverse, immunosuppressive TME composition in comparison to those with negative interim EBV levels. Disease progression was associated with decreased memory B cells and memory CD4$^+$ T cells, suggesting that a suppressed TME is an important mechanism of NKTCL chemotherapy resistance (Figure 1).

Despite the favorable treatment outcomes found in this trial, patients with relapsed / refractory or advanced stage NKTCL continue to incur dismal outcomes. Interim EBV viremia is strongly associated with long-term outcomes, representing a biological surrogate for poor chemotherapy response, specifically asparaginase. This information should be incorporated into the design of treatment trials for NKTCL patients known to bear an unfavorable outcome, independent of disease stage at presentation. For instance, the ongoing study for advanced-stage NKTCL in children, adolescents, and young adults modifies post D-SMILE (daratumumab + modified SMILE) induction treatment using a checkpoint inhibitor (pembrolizumab) for patients with less than complete response (*clinicaltrials.gov 03719105*).

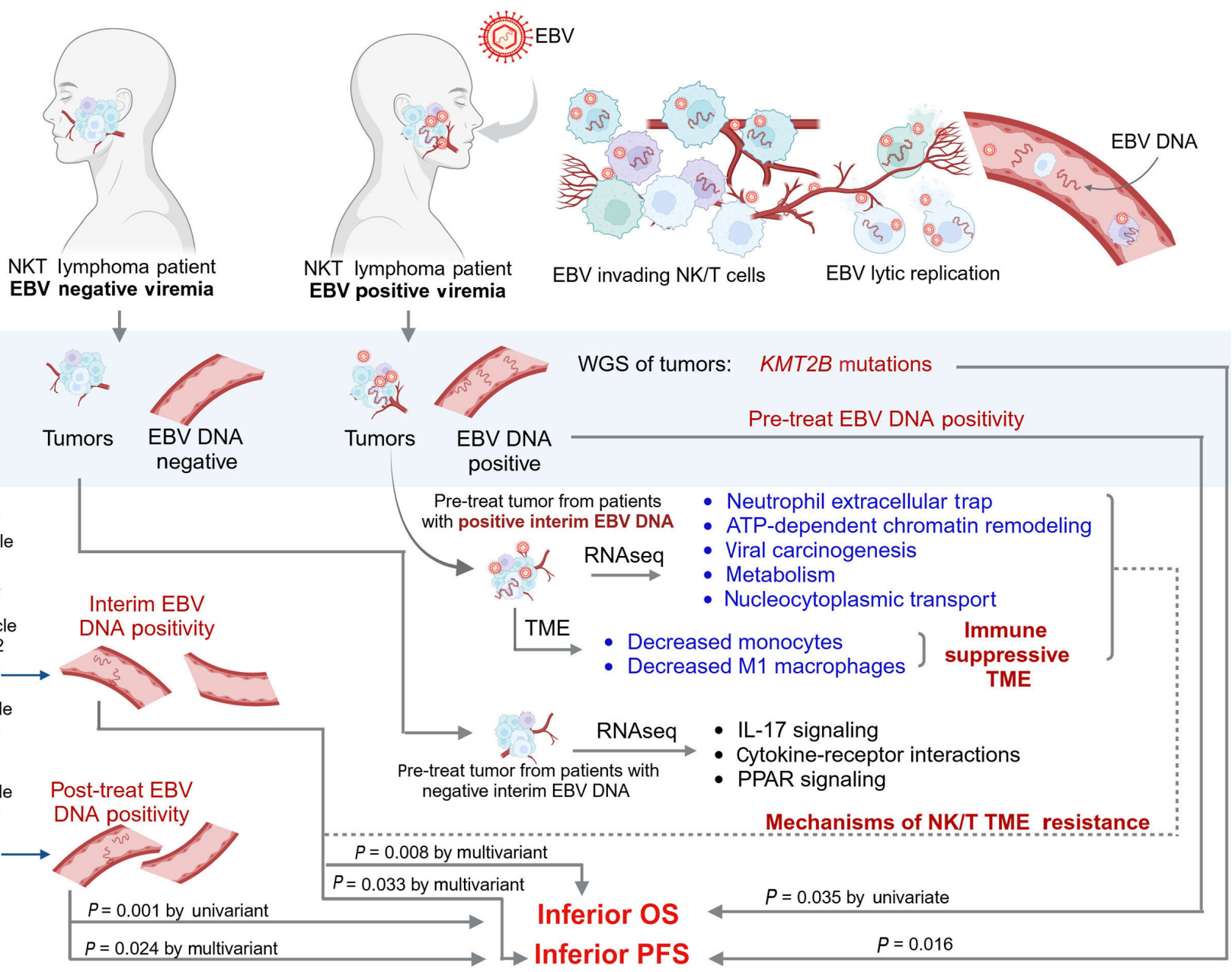

Figure. 1. Epstein-Barr virus viremia is associated with natural killer cell / T-cell lymphoma malignant transformation and Epstein-Barr virus viremia persistence following therapy. Epstein-Barr virus (EBV) viremia is associated with natural killer (NK) cell / T-cell lymphoma malignant transformation and Epstein-Barr virus viremia persistence following therapy is significantly associated with inferior overall response (ORR), progression-free survival (PFS) and overall survival (OS). ESA: etoposide, dexamethasone, and pegaspargase; MESA: methotrexate, etoposide, dexamethasone, and pegaspargase; RNAseq: RNA sequencing; TME: tumor microenvironment. This figure was created with BioRender.com

Table 1. Potential targeted treatment approaches in natural killer cell / T-cell lymphoma.

Genetic alterations	Signal crosslink	Drug class
Immunotherapy		
PD-1, PD-L1, CTLA-4	PD-1/PD-L1, LMP1, JAK-STAT, NF-κβ	Check-point inhibitors (pembrolizumab, nivolumab, ipilimumab)
EBV antigens (LMP1/LMP2)	NF-κβ, PD-L1	EBV-CTL
CD38	Calcium, BCR, TLR	Anti-CD38 monoclonal antibodies (daratumumab), CD30 CAR-T cells
CD30	NF-κβ, MAPK	Anti-CD30 monoclonal antibodies (brentuximab vedotin), CD30 CAR-T cells
CD52	IL-15	Alemtuzumab
CCR4	JAK-STAT, NF-κβ, PI3K	Anti-CCR4 monoclonal antibody
Immunomodulation		
Anti-inflammatory	IL-2, NF-κβ	Thalidomide, lenalidomide
Epigenetic alterations		
Hypermethylation	Cell cycle regulators, tumor suppressors	Hypomethylating agents
Histone modifications	*EZH2*, NF-κβ	Histone deacetylase inhibitors
Tyrosine kinase inhibition	MAPK, PI3K, JAK-STAT	Small molecule TKI VEGFR, PDGFR

BCR: B-cell receptor; CAR-T: chimeric antigen receptor T-cell therapy; CD: cluster of differentiation; EBV-CTL: Epstein-Barr-specific cytotoxic T lymphocytes; CTLA-4: cytotoxic T-lymphocyte associated protein 4; CCR4:L: C-C chemokine receptor type 4; IL: interleukin; JAK-STAT: Janus kinase and signal transducer and activator or transcription; LPD-1: programmed cell death protein 1; MAPK: mitogen-activated protein kinase; NF-κβ: nuclear factor kappa-light-chain-enhancer of activated B cells; PDGFR: platelet-derived growth factor receptor; PD-L1: programmed death-ligand 1; PI3K: phosphoinositidine 3-kinase; TLR: toll-like receptors; VEGFR: vascular endothelial growth factor receptor.

Disease assessment uses functional imaging, but EBV viremia is being tracked at interim time points, in addition to other biologic studies.[8] It will be interesting to see if similar biologic patterns are found in a younger cohort, from a different geographic area, and with advanced stage NKTCL. Our current knowledge indicates that the success of NKTCL therapy may depend on the use of drugs that target the EBV and/or the direct immune / TME downstream effects triggered and maintained by the virus (Table 1). Targeted immunotherapy with monoclonal antibodies (e.g., daratumumab), TME modulation (e.g., checkpoint inhibitors), or EBV T-cell immunity restoration (e.g., donor-derived or autologous EBV-specific T cells) have been shown to be effective in patients with a variety of EBV-driven lymphomas, persistent EBV-associated infections or lymphoproliferations.[8-10] In an attempt to break the long-term relationship between EBV and NKTCL, we will need to design and investigate adjunctive therapies that will circumvent EBV-associated resistance and its effect with the NKTCL TME.

Disclosures

No conflicts of interest to disclose.

Contributions

ACX, YL and MSC wrote and reviewed the editorial.

Acknowledgments

The authors would like to thank Virginia Davenport, RN, for her assistance in the preparation of this manuscript.

Funding

This work was supported by the FDA RO1FD006363.

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