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**Introduction:** Patients with Epstein-Barr virus-positive (EBV+) lymphoma are currently faced with challenging outcomes and represent an unmet medical need. Clinical outcomes in this population may be inferior to the EBV− counterpart in different lymphoma subtypes, including Peripheral T-Cell Lymphoma (PTCL). With a novel mechanism of action, nanatinostat (Nstat, a potent Class-I histone deacetylase inhibitor) induces expression of the lytic BGLF4 protein kinase, which activates the nucleoside analog ganciclovir (GCV), derived from valganciclovir (VGCV) via phosphorylation. Incorporation of phospho-GCV into cellular DNA results in termination of DNA synthesis causing apoptosis. **Materials and methods:** NAVAL-1 (NCR05011058) is an adaptive Phase 2, open-label, single-arm, two-stage, basket trial. Each lymphoma subtype cohort where ≥2 of 10 patients in Stage 1 responded to Nstat (20 mg orally once daily, 4 days/week) and VGCV (900 mg orally once daily, 7 days/week) continued to enroll 11 patients in Stage 2, for a total of 21 patients in each cohort. Efficacy and safety data from the 21-patient relapsed/refractory (R/R) EBV + PTCL cohort are presented herein. **Results:** As of 28 June, 2024, the investigator-assessed overall response rate (ORR), as assessed by Cheson 2007, in 21 patients treated with Nstat+VGCV was 33% (with a median duration of response that has not yet been reached) with a complete response rate (CRR) of 19% in the intent-to-treat population (ORR 41% and CRR 24% in the efficacy-evaluable population), including 2 patients who were able to proceed to allogeneic hematopoietic stem cell transplant. Patients receiving the combination in the second-line treatment setting had higher ORR (60%), with a CRR of 30% (efficacy-evaluable ORR 67% and CRR 33%). Most TRAEs have been hematological or gastrointestinal in nature and primarily Grade 1-2 in severity, and most Grade ≥3 TRAEs have been generally manageable or reversible except for one Grade 5 TRAE of sepsis in the context of severe cytopenias. Serious TRAEs have included influenza, pneumonia, upper respiratory tract infection, pancytopenia and sepsis (1 each). **Conclusion:** Nstat+VGCV is emerging as a promising, generally well-tolerated treatment for patients with R/R EBV + PTCL, particularly in the second-line treatment setting. Enrollment in the PTCL expansion is ongoing.

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## UNVEILING THE PROGNOSTIC CHALLENGES OF NODAL PERIPHERAL T-CELL LYMPHOMAS: A MULTICENTER REAL-WORLD STUDY

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**Introduction:** Peripheral T-cell lymphomas (PTCL) are a rare group of malignancies derived from mature T-cells or natural killer cells, characterized by significant clinical-biological heterogeneity despite being grouped together. These entities have unique clinical, morphological, phenotypic, and molecular signatures. The predominantly nodal presentation group includes the histological variants ALK-positive anaplastic large cell lymphoma (ALK1+ ALCL), ALK-negative anaplastic large cell lymphoma (ALK1- ALCL), angioimmunoblastic T-cell lymphoma (AITL), and PTCL, not otherwise specified (PTCL-NOS). The central pillar of treatment for this subgroup of lymphomas is based on anthracycline-containing polychemotherapy regimens and upfront consolidation with autologous hematopoietic stem cell transplantation, although unfavorable outcomes such as primary refractory disease and early relapses are still common, except for the ALK1+ ALCL subgroup. **Methodology:** Hence, a multicenter, real-world, ambispective study was conducted, involving reference institutions in Brazil and two in the USA, to evaluate the main clinical-demographic characteristics associated with the outcomes of 179 patients diagnosed with nodal PTCL. **Results and discussion:** Individuals with nodal PTCL often presented at diagnosis with unfavorable clinical features, including a high frequency of advanced disease (stages III and IV), high tumor burden, poor performance status (ECOG ≥ 2 points), and frequent allocation in high-risk categories of the IPI and PIT prognostic indices. Patients with nodal PTCL included in this study globally exhibited low Complete Response rates, as well as shortened Overall Survival (OS) and Progression-Free Survival (PFS). In this cohort, we did not identify a robust survival benefit from the intensification of the CHOP regimen with the addition of etoposide (CHOEP protocol) or with BV-CHP. Age ≥ 60 years, ECOG ≥ 2, and lack of complete remission after primary therapy centered on CHOP-like chemotherapy were identified as independent prognostic factors associated with worse survival in this cohort represented by the four main histopathological subtypes of nodal PTCL. **Conclusion:** This analysis demonstrated a high frequency of unfavorable clinical features and poor OS and PFS outcomes in patients with nodal PTCL, regardless of the frontline chemotherapy regimen.

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## REVEALING HIDDEN PATTERNS: HOW UNSUPERVISED MACHINE LEARNING AND MCA PREDICT SURVIVAL IN NODAL PERIPHERAL T-CELL LYMPHOMA PATIENTS

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Unsupervised machine learning techniques are employed to understand patterns and behaviors of variables in databases. Multiple Correspondence Analysis (MCA), an extension of correspondence analysis, can be used to verify the association of categorical variables and their categories. In this study, we evaluated the relationship between clinical-demographic variables of 154 patients with nodal peripheral T-cell lymphoma (PTCL) to understand how these variables relate to the unfavorable clinical outcome, death. **Methodology:** MCA was used to reduce the dimensionality of the real world database by creating two dimensions, 1 and 2, which were subsequently categorized into group 1 and group 2. Dimension 1, comprising ECOG, IPI, treatment, overall response, remission, and bone marrow transplant, represented about 30% of the total observed variance. Survival analysis was conducted to assess the association between these groups and overall survival (OS) and mortality rate. **Results:** The categories of dimension 1, group 1 and group 2, were associated with OS and mortality rate, with group 1 being associated with 5.5 months (95% CI: 2.70 − 8.40) of OS, while group 2 had a survival time of 277.20 months (95% CI: 91.21 − 463.12). Moreover, the mortality rate in group 1 was 87% (n = 67) and in group 2 it was 36% (n = 28) ($p < 0.001$). The risk of death for group 1 was 11.11 times (95% CI: 9.75-18.30; $\beta$= 2.41; $p < 0.001$). **Discussion:** These findings indicate a significant disparity in survival outcomes based on the clinical-demographic profiles of the patients. Group 1, characterized by poorer clinical indicators, exhibited substantially shorter OS and higher mortality rates. The ability of MCA to effectively reduce dimensionality while preserving the clinical relevance of the variables underscores its utility in identifying key prognostic factors. **Conclusion:** The MCA technique was effective in reducing the dimensionality of the database, maintaining the clinical characteristics of the variables robustly for use in Cox regression. This approach can aid in the identification of high-risk patient groups and inform treatment strategies aimed at improving clinical outcomes.

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## IDENTIFICATION, QUANTIFICATION, AND MONITORING OF CIRCULATING TUMOR DNA IN PERIPHERAL BLOOD IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA USING THE Z-SCAN TECHNIQUE

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**Introduction:** Circulating free DNA (cfDNA), particularly circulating tumor DNA (ctDNA), has emerged as a pivotal tool for diagnosis, response assessment, and monitoring of various malignancies. However, in most cancers, it has yet to be incorporated into clinical practice due to the lack of reproducible and widely accessible methodological standardization. In this context, numerous studies have been conducted to achieve such standardization. The purpose of this study was to evaluate the quantification of cfDNA and the identification of plasma ctDNA using the Z-scan technique in patients with diffuse large B-cell lymphoma (DLBCL). **Methods:** Peripheral blood samples were prospectively collected from DLBCL patients at diagnosis, after the fourth treatment cycle, and at the end of R-CHOP-like treatment. Simultaneously, samples from healthy individuals matched by sex and age were collected. After obtaining cfDNA, its concentration was assessed using Nanodrop, Qubit, Bioanalyzer, and Z-scan equipment. The results were compared and correlated with the clinical characteristics of the patients. **Results:** From January 2018 to December 2022, 54 DLBCL patients were recruited, with a median age of 58 years (ranging from 21 to 91 years), 33 (62.9%) of whom were female. The overall response rate of the cohort was 68.52%, with a median follow-up of 24.6 months, showing an overall survival of 32 months and event-free survival of six months. The concentrations of cfDNA varied significantly among the different reading methodologies used. The peak-to-valley distance (Theta values - Θ) of cfDNA from patients at diagnosis (mean of 0.438) obtained in the Z-scan was statistically distinct between the control group (background) and patients at different collection points. The peak-to-valley distance (Θ) of cfDNA samples collected at diagnosis was higher than that of the control group (background), p = 0.068, those collected after cycle 4 (mean 0.33), p = 0.016, and after treatment completion (mean 0.33), p = 0.0005. Several cut-off points for "Θ" were tested to identify the best discriminatory value between DLBCL and healthy control, with a sensitivity of 64.71% (95% CI: 50.99% to 76.37%) and specificity of 86.61% (95% CI: 62.86% to 93.02%) for $\Theta > 0.406$. No correlations were found between "Θ" values and the clinical and demographic characteristics of the patients. **Conclusion:** The Z-Scan technique was able to distinguish DLBCL patients from healthy controls, as well as samples obtained during and after treatment from those collected before the start of anti-lymphoma therapy. We hypothesize that this discrimination was possible because the Z-scan technique may have been capable of distinguishing ctDNA from cfDNA.

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## TRANSPLANTE ALOGÊNICO DE CÉLULAS TRONCO HEMATOPOIÉTICAS COMO ÚNICO TRATAMENTO CURATIVO PARA DOENÇA LINFOPROLIFERATIVA T/NK HIDROA VACINIFORME-LIKE EBV POSITIVO: UM RELATO DE CASO

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