(PB3735) A SYSTEMATIC ASSESSMENT OF DLBCL CELL-OF-ORIGIN CLASSIFICATION PERFORMANCE EVALUATING NON-INFERIORITY OF HANS IHC TO GEP

Topic: 19. Large B cell lymphomas - Clinical

Ash Alizadeh*[1], Anirban Basu[2], Shady Gendy[3], Brad Thomas[3], Manikanta Dasari[4], Girish Venkataraman[5]

[1]Stanford University School of Medicine, Division of Oncology, Department of Medicine, Stanford Cancer Institute and Institute of Stem Cell Biology & Regenerative Medicine, Stanford, CA, United States of America; [2]University of Washington, The CHOICE Institute, Seattle, WA, United States of America; [3]AstraZeneca, Gaithersburg, MD, United States of America; [4]Indence Health, Kolkata, India; [5]University of Chicago Medicine, Department of Pathology, Chicago, IL, United States of America;

Background

Multiple international guidelines deem Cell-of-origin (COO) classification essential for diagnosis of diffuse large-B-cell lymphoma, not otherwise specified (DLBCL-NOS). Yet despite established prognostic value and potential predictive value for therapy selection, there is no consensus on the optimal method. Gene expression profiling (GEP) on fresh-frozen (FF) or formalin-fixed paraffin-embedded (FFPE) tissue is often viewed as the reference, but universal GEP is hampered by access and tissue constraints. In contrast, easy access to FFPE, a simpler platform, and a quick turnaround time have favored Immunohistochemistry (IHC) testing by Hans Algorithm (CD10/BCL6/MUM1), although its performance vs GEP remains debated, and prior comparisons are constrained by key methodological limitations. Reported accuracy varies widely across studies due to differences in study design and patient population, inclusion of heterogeneous pathologic subtypes (beyond pure DLBCL-NOS), frequent differential verification bias, particularly when GEP-unclassified cases are excluded, as well as reliance on a single GEP platform as the comparator despite documented platform and specimen variability.

Aims

We established “ENHANSEMENT”, a novel meta-analytical framework for direct, case-level comparisons of COO classification performance in DLBCL-NOS by Hans IHC vs pooled GEP. The primary endpoint was to test non-inferiority (NI) of diagnostic accuracy for Hans vs GEP at a prespecified margin (10%). Secondary objectives evaluated non-Germinal Center B-Cell Like sensitivity, specificity, and positive/negative predictive value (PPV/NPV).

Methods

We conducted a systematic literature review to identify studies reporting case-level COO by Hans and/or GEP in DLBCL-NOS, using PRISMA-DTA (Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies) guidance. Two complementary datasets were assembled: (i) studies comparing Hans IHC to GEP, and (ii) studies comparing GEP platforms; both datasets were reviewed for completeness by a consortium of domain experts. With no perfect gold standard, we used a Bayesian latent class model as the primary approach to jointly synthesize both evidence streams, treat true COO as latent, and estimate Hans and pooled GEP performance while accounting for study and platform-level heterogeneity. Hans was defined as non-inferior to GEP if the upper bound of the 95% credible interval (CrI) for the difference in performance metrics did not exceed the prespecified 10% NI margin, aligned with accepted FFPE/FF GEP variability, College of American Pathologists’ ≥90% concordance benchmark, diagnostic NI precedents and reviews reporting ~10% NI margins.

Results

19 studies (Fig.1) comprising 2,247 tumors were included: 16 IHC-GEP, 8 GEP-GEP, 4 both. Using latent truth as reference, accuracy was 90% (95%CrI:87-93) for Hans and 95% (93-96) for GEP. The difference of 4.5% (1-8) met the 10% NI margin. Secondary endpoints including specificity and PPV also met the NI margin, while sensitivity and NPV just exceeded the margin with difference of 6.5% (2-11) and 6.4% (2-11), respectively.

Summary/Conclusion

In this largest meta-analysis of DLBCL-NOS classification methods, COO classification by Hans IHC is non-inferior to GEP at the prespecified margin for diagnostic accuracy, reinforcing the widely used and broadly accessible Hans IHC as a reliable method for guideline-recommended COO classification in DLBCL-NOS.

Fig.1: PRISMA flow diagram