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Lymphomas

CLINICAL IMPACT OF UNTARGETED BASELINE PLASMA METABOLOMICS IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma, characterized by marked biological heterogeneity and variable outcomes. Despite the integration of circulating tumor DNA (ctDNA), molecular clusters identified on the liquid biopsy and PET/CT parameters, early identification of refractory/relapsing patients is still problematic. Metabolomics offers an integrative snapshot of tumor and host biology. This study investigated the plasma metabolomic profile of newly diagnosed DLBCL, its association with clinical outcomes, and its integration with ctDNA and PET/CT features

Methods: The study included a training cohort of 96 newly diagnosed DLBCL patients treated with R-CHOP. Baseline plasma samples underwent untargeted metabolomic profiling using high-resolution bidimensional gas chromatography–-mass spectrometry. ctDNA levels were quantified with CAP-P-Seq. Baseline PET/CT scans for total metabolic tumor volume (tMTV) assessment were available for 87 patients. A validation cohort of 42 R-CHOP-treated DLBCL was also analyzed. Maximally selected rank statistics identified optimal cutoffs predicting progression-free survival (PFS) for each metabolite, ctDNA, and tMTV.

Results: Untargeted metabolomics identified 281 metabolites. Based on 24-month PFS, 10 metabolites were differentially expressed between progressive (n = 34) and non-progressive (n = 62) patients. Among these, 4-hydroxybenzeneacetic acid (4-HPA) and 2-hydroxybutyric acid (2-HB) were consistently upregulated in progressive cases and validated in the validation cohort. High 4-HPA and 2-HB levels correlated with inferior 40-month PFS (training: p=0.027 and p=0.02; validation: p=0.002 and p=0.003, respectively). In the training cohort, both metabolites refined outcome prediction among ctDNA-low patients: cases with high 4-HPA (N=5) or 2-HB (N=7) had significantly shorter PFS than those with lower levels of 4-HPA (N=49) and 2-HB (N=47) (p<0.0001 and p=0.041, respectively). Similarly, among tMTV-low patients, higher 4-HPA (N=6) and 2-HB (N=7) displayed worse outcomes than patients with lower 4-HPA (N=52) and 2-HB (N=51) (p=0.00076 and p=0.052, respectively).

Conclusions: Baseline plasma metabolites harbor promising prognostic value in newly diagnosed R-CHOP-treated DLBCL. Baseline 4-HPA and 2-HB levels are associated with shorter PFS and further refine the prognosis of a subset of patients who were incorrectly classified as low-risk based on ctDNA levels and tMTV. 4-HPA may reflect the potential contribution of microbiome changes to disease course and response to therapy, while 2-HB may capture the prognostic relevance of oxidative stress and metabolic dysregulation in DLBCL.

LYMPHOMAS

Figure 1