XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari

Lymphomas

FEASIBILITY OF IMMUNOGLOBULIN GENE REARRANGEMENT TRACKING ON CIRCULATING TUMOR DNA AS AN OUTCOME PREDICTOR IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA

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Introduction: Primary mediastinal B-cell lymphoma (PMBCL) can be cured in most patients. Current efforts aim at identifying good risk patients that can avoid radiotherapy after first-line immunochemotherapy and the few high-risk patients who fail the first-line treatment and can be rescued with novel immunotherapies. Circulating tumor DNA (ctDNA) analysis is a promising non-invasive tool to monitor minimal residual disease (MRD) in large B-cell lymphoma (LBCL) by immunoglobulin (IG) gene rearrangement. No data is currently available for PMBCL. This study aims to evaluate the feasibility and prognostic value of ctDNA-based IG-MRD analysis in PMBCL patients. Methods: In a monocentric, non-profit, observational prospective study, plasma samples from consecutive adult PMBCL patients undergoing first or second line therapy were prospectively collected since March 2023. Plasma samples were collected at baseline, interim (6th week), end-of-treatment (EOT). For patients receiving CAR-T cells, baseline sample was collected before lymphodepletion and at 28 days from CAR-T infusion. Cell-free DNA (cfDNA) was extracted, quantified and analyzed by next-generation sequencing (NGS) using the LymphoTrack IGH FR2/FR3 and IGK assays on MiSeq instrument. For each patient, IGH/IGK clonality will be assessed in paired gDNA samples extracted from FFPE biopsies. Clinical data were prospectively collected. The primary objective was the detection rate of clonal IG rearrangements on baseline ctDNA. Results: 19 PMBCL patients have been so far enrolled, median age at diagnosis was 34 years, 11/19 were female; of them, 5 patients underwent CAR-T cell therapy. The median circulating cfDNA yield at diagnosis was 1.3 ng/µl (range 0.31–3.9), in the CAR-T setting was considerably lower. Sixteen out of 19 baseline samples were screened and IGH and/or IGK clonal rearrangements were successfully identified in all cases, with 1.4 average number of clonal sequences identified per patient. Median clonal frequency was 10.9% (CI 2.6-95.8) clonal sequence's average length was 93 bp and 188 bp for IGH and IGK, respectively; V-J rearrangement’s average identity was 89%. Interim and EOT samples analysis are currently ongoing to evaluate the prognostic value of ctDNA MRD dynamics. Clinically, after a median follow-up of 18 months, 3 progressions and 1 death were observed.
Conclusions: Preliminary analysis demonstrates the feasibility and high rate of clonal IG detection on ctDNA before treatment in PMBCL, despite its typical confinement to the mediastinum, supporting the biological relevance of liquid biopsy in this entity. Ongoing analyses at interim and EOT will clarify whether ctDNA clearance can predict PET/CT response and early relapse. If validated, ctDNA IG-MRD monitoring could represent a non-invasive biomarker for early treatment adaptation and improved risk stratification of PMBCL patients, including those considered for CAR T-cell therapy.