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POSTER ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Immunomodulatory Effects of Chemo-Immunotherapy ± Idelalisib in Chronic Lymphocytic Leukaemia (CLL)

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Introduction: Chronic lymphocytic leukaemia (CLL) is characterised by a dysfunctional immune profile. However, the precise impact of therapy on this altered immune state, both short and long term, remains unclear. The collection of pre-treatment and longitudinal blood samples in the NCRI phase III RIAltO trial (NCT01678430) offered a unique opportunity to address this question in the context of frontline chemo-immunotherapy (CIT) containing bendamustine or chlorambucil. The factorial randomisation to idelalisib versus placebo also provided a framework for investigating the immunomodulatory effects of PI3Kδ inhibition in this setting.
Methods: We conducted mass cytometry analysis on samples obtained from CLL patients enrolled in the RIAltO trial. Patients were randomly assigned to receive ofatumumab plus either bendamustine or chlorambucil, with or without idelalisib. Samples were collected before treatment and at early (median 5.9 [IQR 5.7 - 6.4] months) and late (18.5 [16.1 - 22.6] months) post-treatment timepoints. Three healthy controls (HC) were included for comparison. CD3 $^{+}$ T cells were analysed using a customised CyTOF panel comprising 36 markers. Uniform manifold approximation and projection (UMAP) and manual gating analysis were utilised to evaluate global and specific T-cell changes.
Results: In all, 177 samples from 79 CLL patients, obtained before or after CIT, were analysed. Baseline characteristics were similar between the different treatment arms. Compared to HC, treatment-naïve CLL patients exhibited a distinct T-cell profile with increased regulatory T cells, decreased naïve and central memory (CM) cells, elevated effector memory (EM) cells, reduced non-senescent cells, and increased expression of HLA-DR, PD-1, TOX, T-bet, and Eomes. Following CIT, the T-cell profile was significantly altered but remained distinct from that of HCs. CIT-induced changes persisted at the late post-treatment timepoint, indicating a sustained effect. Analysis of specific T-cell populations showed that, although some CLL-associated features became less prominent following CIT (expression of PD-1, TOX and TIGIT), most were enhanced (shift from naïve and CM cells towards a terminal effector phenotype; shift from a non-senescent to a terminally senescent phenotype; increased HLA-DR and T-bet expression). The post-treatment immune profiles were similar in patients receiving bendamustine or chlorambucil. Despite its immunomodulatory effects when used as a single agent, idelalisib also induced minimal additional changes. Furthermore, the post-treatment immune profile was similar in patients achieving minimal residual disease (MRD) negativity versus those who remained MRD positive, suggesting a direct pharmacodynamic effect. Finally, non-metric multidimensional scaling (NMDS) analysis demonstrated that CIT shifted the overall CLL-associated immune profile further away from that of HC, and that the shift was independent of chemotherapy allocation, idelalisib, or the level of CLL cytoreduction achieved.
Conclusion: CIT results in profound immune changes that persists up to 18.5 [16.1 - 22.6] months following treatment. Furthermore, the overall effect of these changes further differentiates the CLL-associated immune profile from that of HC, deepening the existing T-cell dysfunction irrespective of chemotherapy choice, or the addition of idelalisib. Our study has important potential implications for patients receiving CIT in a range of clinical settings and supports the move towards more targeted agents that are less likely to cause indiscriminate immune perturbation.

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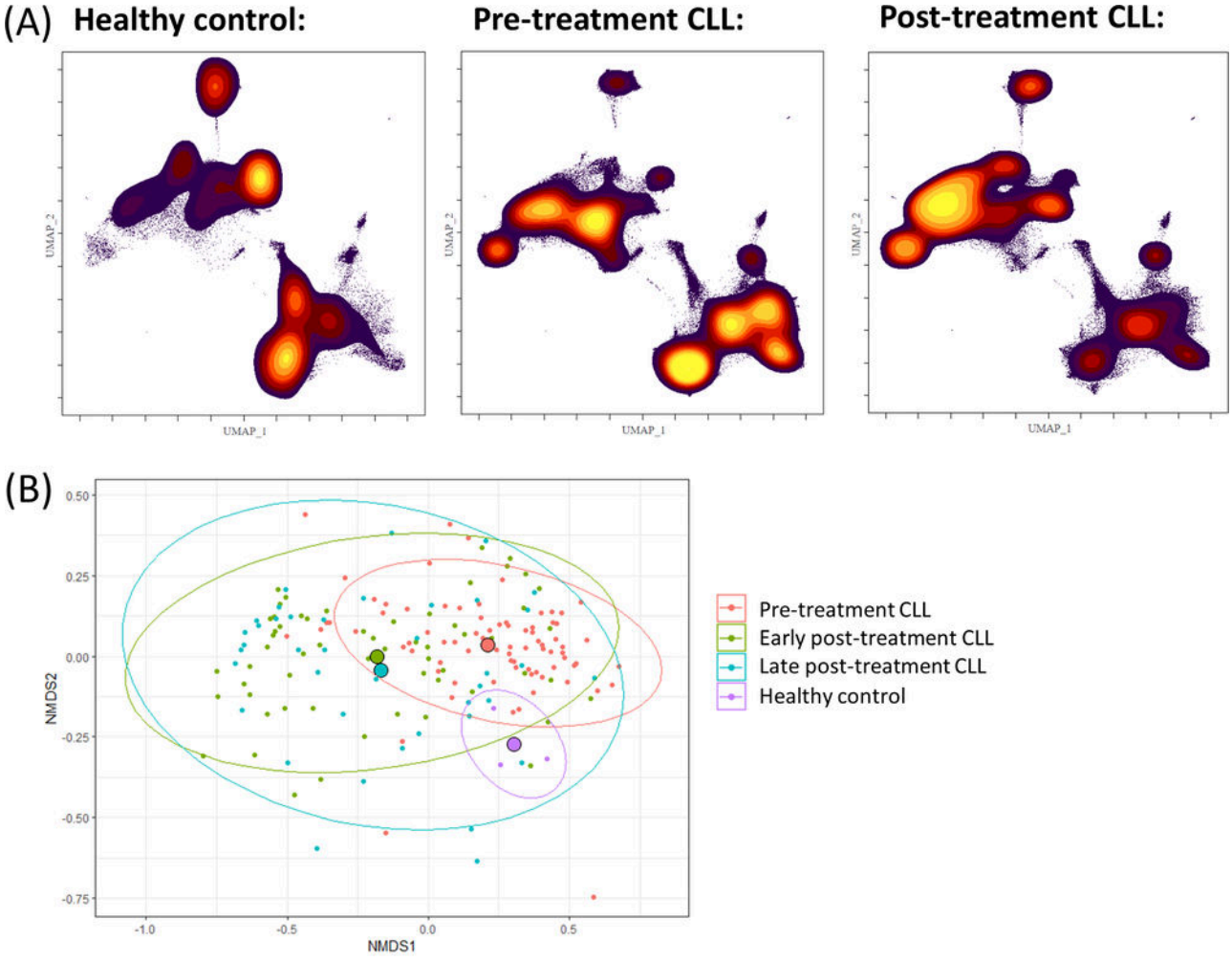

Figure 1: CD3+ T cell profile of patients with CLL prior to and following CIT, compared to that of healthy controls (HCs). (A) Contour plots of UMAP representing CD3⁺ T cells from HCs (left) and CLL patients at pre- (mid) and post-treatment (left). (B) NMDS plot of median CD3⁺ expression in all analysed samples. Median centroid and ellipse was assigned computationally for each subgroup.

Figure 1

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