P1283 CIRCULATING IMMUNE CELLS IN CLASSICAL HODGKIN LYMPHOMA IN RELATION TO TUMOR BURDEN AND TREATMENT

**Topic:** 20. Lymphoma Biology & Translational Research

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**Background:** Classical Hodgkin lymphoma (cHL) has a peculiar histology with pathognomonic Hodgkin and Reed-Sternberg (HRS) cells representing only a small fraction of the tumor mass. HRS orchestrate a lymphocyte-dominated tumor microenvironment (TME) that supports their survival and growth, suggesting that even circulating immune cells might be affected.

**Aims:** To comprehensively characterize circulating lymphocytes in cHL patients (pts) in relation to their frequency in the tumor tissue, the tumor load and the effect of standard first-line treatment.

**Methods:**
Peripheral blood (PB) samples were obtained from 48 consecutive newly diagnosed pts before start of treatment (BL), right at the end of treatment (EoT) and at 6 months’ follow-up after EoT (FU). Twenty-eight pts had limited-stage (I-IIA) (LIM) and 20 had advanced-stage (IIB-IV) (ADV) disease. All the pts in the FU analysis were in complete remission. Twenty healthy individuals were included as controls. Cells from PB and lymph node (LN) biopsies were freshly analyzed by flow cytometry. Plasma concentrations of CCL17/TARC were measured by Enzyme-Linked ImmunoSorbent Assay.

**Results:**
At BL, the numbers of B cells were lower in both LIM and ADV cHL compared to controls (median 0.075 (p<0.0001) and 0.067 (p<0.0001) vs. 0.17 x10^9 cells/L, respectively), while T cells were normal. Higher frequencies of intracellular Ki67 expression were observed in LIM and ADV cHL pts compared to controls, among CD4+ (median 2.77 (p=0.0001) and 3.36, (p=0.0004) vs. 0.92 %, respectively) and CD8+ T cells (median 1.85 (p=0.0009) and 3.66 (p=0.0001) vs. 0.91 %, respectively). PD-1+CD4+ T cells were higher in LIM cHL than in controls (median 31.75 vs. 23.05 %, respectively, p=0.0030), while PD-1+CD8+ T cells were higher in both LIM and ADV cHL (median 32.05 (p=0.0041) and 32.20 (p=0.0135) vs. 21.15 %, respectively). CD8+ naive T cells (T_N) cells were lower in LIM and ADV cHL than in controls (median 27.40 (p=0.0005) and 20.15 (p=0.0003) vs. 53.25 %, respectively).

Advanced-stage pts had less NK cells than controls (median 0.14 vs. 0.20 x10^9 cells/L, respectively, p=0.0135). The plasma concentration of CCL17/TARC was elevated in both LIM and ADV cHL compared to controls (median 5256 (p=0.0002) and 9165 (p<0.0001) vs. 61.03 pg/mL, respectively) (Figure 1).

The frequencies of T and B cells positively correlated between the PB and LN compartments (r=0.3855, p=0.0243, and r=0.5203, p=0.0016, respectively).
Patients with a high inflammatory status (i.e. ESR ≥50) had higher percentages of PD-1+CD4+ T<sub>N</sub> cells and lower percentages of CD4<sup>+</sup> effector memory (T<sub>EM</sub>) cells, NKG2D<sup>+</sup> CD56<sup>dim</sup> NK cells and total NK cells in their PB. Pts with a high tumor burden (i.e. bulky tumor and/or ≥2 nodal sites involved and/or stage IV) had higher plasma levels of CCL17/TARC, higher percentages of CTLA-4+CD4<sup>+</sup> T cells, activated regulatory T (Treg) cells, Ki67<sup>+</sup> CD4<sup>+</sup> T cells and Th2 cells in their PB.

T-cell exhaustion and NK-cell depletion were reversed by standard first-line treatment and CCL17/TARC concentrations also dropped back to control levels.

Pts who received radiotherapy (RT) involving the mediastinum had lower T-cell numbers, specifically Th2 cells, CD4<sup>+</sup>T<sub>N</sub> cells and Tregs, at EoT and FU than those who were not subjected to RT.

**Summary/Conclusion:** Immunosuppression of lymphocytes in the TME of cHL might be reflected in the PB. Most immunological changes are reverted after successful standard primary treatment. Patients who receive RT involving the mediastinum have a prolonged T-cell deficit and might benefit from longer Pneumocystis pneumonia prophylaxis.