Complex evaluation of immune defects in patients with chronic lymphocytic leukemia

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Abstract of dissertation thesis

Chronic lymphocytic leukemia (CLL) is associated with significant combined immunodeficiency. Amongst most important immune defects are hypogammaglobulinemia and changes in relative and absolute counts of different lymphocyte populations and subsets. As consequence of these changes, there can be higher frequency of infections and progression of CLL itself. The impact of chemoimmunotherapy (CIT) on immunoglobulin (Ig) levels and lymphocyte populations has not been extensively studied. In this dissertation thesis, we analysed Ig levels and lymphocyte populations (using flow cytometry) in 45 patients with indolent untreated CLL and 90 patients with progressive disease indicated for treatment. In 58 patients, we evaluated the impact of first-line CIT. For lymphocyte populations' analysis, we had also cohort of 34 healthy controls. Patients with progressive disease had significantly lower levels of all Ig classes and subclasses than patients with inactive disease: IgG, median 6.96 vs. 9.86 g/l, p=0.0001; IgA, median 0.63 vs. 1.53 g/l, p<0.0001; IgM, median 0.36 vs. 0.57 g/l, p=0.0035. After treatment, median IgA increased from 0.59 g/l to 0.74 g/l (p=0.0031). Other Ig classes and subclasses did not change significantly. Lower IgG2 was associated with shorter overall survival in patients with progressive disease (p=0.043) and there was a trend towards shorter time to first treatment in stable patients with lower IgA2 (p=0.056). Amongst cohort with progressive disease, patients with unfavourable prognostic markers (unmutated IGHV genes, *TP53* mutation, and deletion of 11q or 17p) had higher levels of some of the Ig classes and subclasses.

CLL patients had a significant increase of most cell populations in comparison to controls. The progression of CLL was characterized by significantly elevated counts with the exception of a lower percentage of naïve T-cells. After treatment, the percentage of naïve T-cells further decreased at the expense of effector memory T-cells (TEM). In patients with indolent CLL, higher percentages of naïve $CD4^+$ (p=0.0026) and naïve $CD8^+$ (p=0.023) T-cells were associated with a longer time to first treatment. The elevation of $CD4^+$ central memory T-cells (TCM) (p=0.027) and TEM (p=0.003) counts and a higher percentage of $CD4^+$ TEM (p=0.0047), were linked with shorter time to first treatment. In treated patients, the increased regulatory T-cells count was associated with a shorter time to next treatment (p=0.042), while higher $CD4^+$ TCM count with shorter time to next treatment (p=0.035) and a shorter overall survival (p=0.041). Unlike with Ig levels, patients with unfavourable prognostic markers had changes in lymphocyte populations similar to these seen in disease progression.