



SERUM LEVELS OF SELECTED CYTOKINES IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA AND THEIR ASSOCIATION WITH PROGNOSTIC FACTORS AND SURVIVAL

Horacek J.M.^{1,2}, Kupsa T.^{1,2}, Vanek J.¹, Jebavy L.^{1,2}, Zak P.²

¹Department of Military Internal Medicine and Military Hygiene, University of Defence, Faculty of Military Health Sciences, Hradec Kralove, Czech Republic

²Department of Internal Medicine IV – Hematology, University Hospital and Charles University, Faculty of Medicine, Hradec Kralove, Czech Republic



BACKGROUND

Dysregulated production of cytokines has been implicated in the onset and progression of various types of cancer. Better understanding of leukemia microenvironment is essential for development of new treatment approaches.

The aim of this study was to evaluate serum levels of selected cytokines in adult B-cell precursor acute lymphoblastic leukemia (B-ALL) at diagnosis and in complete remission (CR), and their association with acknowledged prognostic factors, relapse-free survival (RFS) and overall survival (OS).

METHODS

A total of 42 *de novo* B-ALL patients (median age 49, range 19–75 years; 28 males, 14 females; all Caucasian) were included in this study. Nineteen patients were BCR/ABL positive. Serum samples were taken at diagnosis and in CR. We used Cytokine IV Array (manufactured by Randox Laboratories Ltd., Crumlin, UK) containing the following analytes: soluble receptor α for IL-2 (sIL-2R α), soluble receptor for IL-6 (sIL-6R), soluble receptor for TNF- α type I (sTNFR-1), soluble receptor for TNF- α type II (sTNFR-2) and Matrix Metalloproteinase-9 (MMP-9). All analytes were measured by biochip array technology on Evidence Investigator analyzer.

Correlations between cytokines, acknowledged prognostic factors (age, WBC count, immunophenotype, BCR/ABL, response to induction therapy), RFS and OS were evaluated separately in both clinical situations.

Statistical evaluation was done by a professional statistician using software R 3.5.3 (R Core Team 2019). Probability values (p) < 0.05 with Bonferroni-Holm correction were considered statistically significant.

RESULTS

At diagnosis of B-ALL, we found significantly higher levels of sIL-2R α , sIL-6R, sTNFR-1, sTNFR-2 and significantly lower levels MMP-9 in comparison with CR (p < 0.001 in all cases). *See Table 1.* Levels of sTNFR-1 correlated with sTNFR-2 at diagnosis and in CR (p < 0.001). In CR, sIL-2R α correlated with sIL-6R, sTNFR-1, sTNFR-2 (p < 0.001) and sIL-6R correlated with sTNFR-2 (p < 0.001).

Table 1. Serum levels of cytokines at diagnosis and in complete remission (CR) of B-ALL

Analytes	Diagnosis	CR	p
sIL-2R α [mcg/L]	1.33 \pm 2.04	0.06 \pm 0.08	< 0.001
sIL-6R [mcg/L]	2.32 \pm 1.70	1.25 \pm 0.80	< 0.001
sTNFR-1 [mcg/L]	0.91 \pm 0.43	0.43 \pm 0.21	< 0.001
sTNFR-2 [mcg/L]	0.95 \pm 0.82	0.37 \pm 0.37	< 0.001
MMP-9 [mcg/L]	25.36 \pm 25.04	50.60 \pm 34.34	< 0.001

BCR/ABL positive patients had higher levels of sIL-2R α at diagnosis (r = 0.484; p = 0.014), but not in CR. *See Figure 1.* Correlations of cytokines with other acknowledged prognostic factors in B-ALL did not reach statistical significance.

In our cohort, CR after 1 cycle of induction therapy was achieved in 88 % of patients, 1-year RFS was 74 % and 1-year OS was 86 %. Serum levels of evaluated cytokines were not associated with achievement of CR after 1 cycle of induction therapy, RFS or OS.

CONCLUSION

Cytokines are an important part of leukemia microenvironment. Our results show that serum levels of all evaluated cytokines are significantly altered in newly diagnosed B-ALL, reflecting activity of the disease. We found statistically significant correlation between BCR/ABL positivity and sIL-2R α levels at diagnosis. So far, we did not find any significant correlations with response to induction therapy, RFS or OS. Further studies with a larger spectrum of cytokines and a longer follow-up will be needed.

Figure 1. Correlation between BCR/ABL positivity and serum sIL-2R α levels at diagnosis of B-ALL

