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CHANGES IN THE METABOLOME OF SERUM AND CEREBROSPINAL FLUID DURING INTENSIVE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

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INTRODUCTION

Metabolomics is a rapidly growing field that accurately reflects the organism's state. In oncology, it is combined with genomics, transcriptomics, and other multiomic methods to investigate new targets for personalized anticancer therapies and detect biomarkers for disease onset, relapse and treatment response.

AIM

To conduct an analysis of the serum and cerebrospinal fluid (CSF) metabolomic profiling according to the clinical and molecular characteristics of acute lymphoblastic leukemia (ALL) at the onset of the disease and during the intensive anti-cancer treatment.

MATERIAL AND METHODS

The metabolomes of peripheral blood serum and CSF were analyzed using gas chromatography-mass spectrometry.

The samples were gathered at the onset (day 1), at specific time points during induction of remission (day 8, 12, 15) and at its end (day 33) as well as during first HD-MTX cycle (day M01, M08, M10).
Twenty-eight children aged 0-18 years (median 7.9) with newly diagnosed ALL, treated according to AIEOP-BFM 2017 protocol in Department of Pediatrics, Oncology and Hematology in Lodz, Poland, between 2019 and 2021, were enrolled.

Metabolomic measurements were performed in Clinical Research Center of the Medical University of Bialystok.

Two peak intensity matrices were obtained, complemented with clinical data, and analyzed statistically followed by pathway analysis.

RESULTS

In total, 70 metabolites were identified in serum and 60 in CSF. Metabolomic analysis at the time of diagnosis did not identify markers of CNS involvement by leukemic cells. Correlations in changes of metabolite intensities between CSF and serum were observed.

The most significant differences in metabolite composition were observed in samples collected before treatment and on the day 33 (end of induction). The conducted pathway analysis revealed that the 27 metabolites with altered intensities are involved in amino acid, glutathione, and glycolysis pathways (Fig.1).

Higher concentrations of 1,5-anhydroglucitol (Fig.2) were observed in ALL patients before treatment compared to day 33 (p=0.0005) and day 1 of HD-MTX (p=0.005).

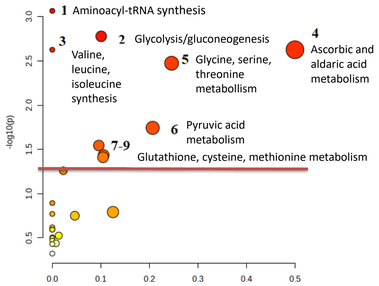


Figure 1. Pathway impact analysis based on metabolites that change intensities between day 1 and day 33 of induction

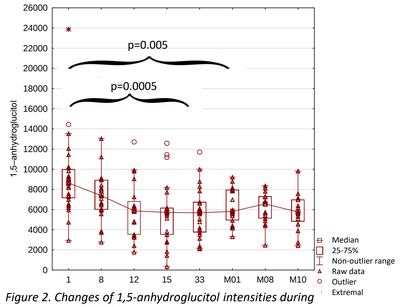


Figure 2. Changes of 1,5-anhydroglucitol intensities during treatment, p=0.00003

The concentrations of presumably microbiome-derived metabolites (short-chained fatty acids, allothreonine) and 2,3-butanediol increased in patients at day 33 (Fig.3-5).

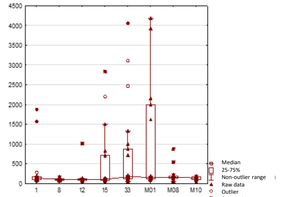


Figure 3. Changes of caprylic acid intensities during treatment, p=0.0001

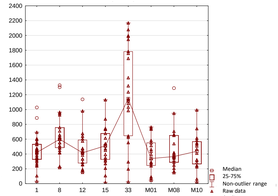


Figure 4. Changes of allothreonine intensities during treatment, p=0.00000

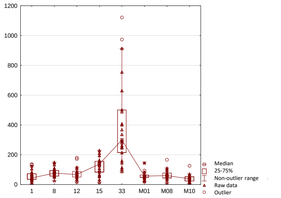


Figure 5. Changes of 2,3-butanediol intensities during treatment, p=0.00000

Patients before treatment and those with positive residual disease differed from children in remission in terms of the intensity of metabolites involved in amino acid metabolism, central carbon metabolic pathways, and urea cycle (Fig.6, Table 1).

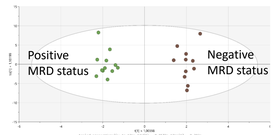


Figure 6. OPLS-DA scatterplot analysis of samples from day 33 regarding MRD status

Metabolite	p(corr)	VIP
Maleic acid	0,54	1,74
2-hydroxyphenylethylamine	0,47	1,6
Valine	0,46	1,6
Isoleucine	0,44	1,53
Urea	0,41	1,49
p-kresol	-0,43	1,41
Methionine	-0,35	1,26
Glycerol-3-phosphate	0,37	1,36

Table 1. OPLS-DA analysis of samples from day 33 regarding MRD status – significant metabolites

Multivariate data analysis (OPLS-DA) at ALL diagnosis revealed that six metabolites had higher intensities in patients with hyperdiploidy (i.e. methionine, stearic acid, caproic acid, urea).
Also six metabolites (i. e. asparagine, methionine, lauric acid, α-ketobutyric acid, capric acid, glycerol-3-phosphate) could discriminate patients with mutations in genes responsible for the proliferation, differentiation, and maturation of lymphocytes (PAX5, CDKN2A, CDKN2B, IZKF1).

CONCLUSIONS

The metabolic fingerprint of patients with lymphoblastic cells reveals changes in main metabolic pathways. The results also indicate metabolic reprograming in cancer cells depending on their genetic features. A significant impact of anti-cancer treatment on metabolome is apparent.
Larger studies are needed to understand disease mechanisms and the observed effects of drugs on cancer cells, the microbiome, and the patient's body.

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