Methotrexate: New research aspects for improved clinical response in childhood acute lymphoblastic leukemia

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Methotrexate (MTX) is the antifolate that has been in clinical use for decades as a component of the curative regimen of children with acute lymphoblastic leukemia (ALL). In recent years, we have witnessed dramatic improvements in survival due to better understanding of a mechanism of action of MTX and evaluating the most effective doses and therapetic schedules. However, large interindividual variability of MTX pharmacokinetics and development of drug resistance are still limiting factors, influencing both the risk of toxicity and clinical outcomes. The aim of this review is to highlight the need for further research in this area.

High doses of MTX (HD-MTX) through 24 hours-intravenous infusion followed by administration of leucovorin rescue are a vital part of contemporary ALL regimens. It has been shown that HD-MTX enhanced formation of MTX active metabolites - polyglutamates (MTXPGs) that accummulate in leukemic blasts and surrogate erythrocytes. Also, it has been demonstrated that after high doses MTX entered the cell not only via reduced folyl carrier but also by passive diffusion. Considering the short plasma half-life of the parent drug and MTXPGs correlation with antileukemic events, great attention has been placed in the monitoring of MTXPGs levels as potential markers for refinement of MTX therapy. Nevertheless, exact mechanisms responsible for defective polyglutamylation and reduced intracellular amounts of MTXPGs have not been fully elucidated. Variations in the genes implicated in polyglutamate efflux transporters may play role in the prolonged elimination of MTX and differences in treatment efficacy. Pharmacogenetics alone and the monitoring of MTXPGs levels in erythrocytes by liquid chromatography–mass spectrometry might have not been enough for accurate predictions of patients' clinical response.

Therefore, thorough *in vitro* experiments of MTXPGs transporters and an analysis of biochemical changes around the MTX pathway would be desirable to fill the gap in current knowledge about MTX and to personalize the use of ALL regimens more effectively and safely.

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Biography

Slavica Lazarevic is from department of Pharmacology, Toxicology and Clinical Pharmacology. Slavica Lazarevic is currently working as a Faculty of Medicine at University of Novi Sad, Serbia.

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