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

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Abstract

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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Introduction:

The treatment result of pediatric intense lymphoblastic leukemia (ALL) has extraordinarily improved in the course of recent decades with the present regimens bringing about a 5-year occasion free endurance (EFS) of around 80 %. This amazing improvement has been to a great extent ascribed to novel prognostic components, including cytogenetic variations from the norm, for example, TEL-AML1 and E2A-PBX1 quality combinations related with great forecast just as MLL quality revisions that present horrible guess. However, the high fix rates accomplished with current treatment conventions are still resembled by roughly 20 % danger of backslide, which is thusly connected with poor guess. The development of backslide is to a great extent inferable from medicate obstruction wonders of leukemic cells. Hence, further advances in understanding the sub-atomic premise basic these medication opposition wonders just as exact expectation of chemotherapy obstruction preceding medication treatment may make ready to beating chemoresistance.

Truly, one of the spines of contemporary ALL treatment is the folate antimetabolite—methotrexate (MTX). Folates are basic chemical cofactors associated with one-carbon digestion, which incorporates a few cell biosynthetic pathways including thymidylate and again purine biosynthesis, amino corrosive digestion, and mitochondrial protein amalgamation. Antifolates strongly restrain a few folate-subordinate chemicals occupied with nucleotide biosynthesis, which prompts discontinuance of DNA replication in the end bringing about cell demise. High-portion (HD)- MTX is utilized as a feature of the focal sensory system (CNS)- coordinated treatment (intrathecal MTX), and MTX is a fundamental part of the support treatment. MTX is prevalently taken up into cells by means of the diminished folate bearer (RFC/SLC19A1), and on account of HD-MTX treatment, additionally by latent dispersion across cell films, in any event somewhat . Upon passage into the cytoplasm, MTX experiences polyglutamylation—an exceptional metabolic transformation catalyzed by folylpolyglutamate synthetase (FPGS). This polyglutamylation, which depends on the successive expansion of numerous glutamate deposits to the γ-carboxyl gathering of the two folates and MTX, guarantees proficient intracellular maintenance just as supports and improves target chemical hindrance. The principle focuses of polyglutamylated MTX are dihydrofolate reductase (DHFR—additionally restrained by MTX monoglutamates), thymidylate

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synthase (TS), and a few proteins associated with purine combination. Then again, a lysosomal glycoprotein—folylpolyglutamate hydrolase (FPGH)— can check polyglutamylation, along these lines expanding the efflux of MTX by the efflux transporters of the ATP-restricting tape superfamily including for instance ABCC1 and ABCG2. By and large, the intracellular amassing of MTX polyglutamates in leukemic cells end up being a significant determinant of the antileukemic movement of MTX in youth ALL patients in vivo. Simultaneously, high grouping of long-chain however not all out MTX polyglutamates was related with hindrance of all over again purine amalgamation. Thusly, a range of adjustments in MTX digestion bringing about its diminished cell collection has been distinguished to initiate MTX opposition and bargain its remedial impact. MTX obstruction has been ascribed to inactivating changes or down-guideline influencing the RFC quality just as expanded degrees of DHFR and TS catalysts along with transformations that decline their fondness for antifolates. Moreover, various polymorphisms in RFC, TS, and DHFR were recently detailed, a few of which were identified with expanded danger of backslide. The cytotoxic impact evoked by MTX is additionally to a great extent affected by FPGS movement. Thus, loss of FPGS work is an entrenched system of protection from MTX and other polyglutamylation-subordinate antifolates in leukemic cells. Differential MTX affectability was demonstrated to be related with a few cytogenetic variations from the norm. Forerunner B cell ALL showing TEL-AML1 or E2A-PBX1 quality combinations were described by diminished degrees of MTX polyglutamates when contrasted with antecedent B cell ALL with typical karyotype, while patients with hyperdiploid karyotype were exceptionally touchy to MTX. Next, to its own cytotoxic impact, MTX is additionally significant in the digestion of different chemotherapeutics, for example, mercaptopurine, utilized routinely in ALL treatment. MTX was appeared to advance the change of mercaptopurine to one of its dynamic metabolites—thioguanine nucleotides—of which high fixation in leukemic cells was related with expanded EFS in leukemia patients. Consequently, it is basic to portray the degree of protection from this significant chemotherapeutic just as the systems hidden this wonder.

The point of the present examination was in this way to figure out which parameters of MTX obstruction are identified with the drawn out clinical result in youth ALL patients rewarded with mix chemotherapy. Towards this objective, we have decided a scope of in vitro parameters related with MTX obstruction in an enormous accomplice of pediatric ALL patients and along these lines surveyed their connection with treatment result just as with clinical qualities.

Keywords: Methotrexate, Thymidylate synthase, Polyglutamylation, MTX therapy, TEL-AML1 or E2A-PBX1

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