Article published online: 2021-06-23

Short Communication

SLC19A1 Polymorphism and Serum Methotrexate in Patients with Acute Lymphoblastic Leukemia

Abstract

Acute lymphoblastic leukemia (ALL) is a common pediatric malignancy. Methotrexate is the widely used chemotherapy for ALL. The polymorphism (rs1051296) of *SLC19A1* is proposed for its effect on serum methotrexate. To explain this observation, the authors hereby studied the interrelationship between *SLC19A1* polymorphism and blood methotrexate level in the patients with ALL. Here, the authors use a quantum chemistry analysis for explaining of this observation.

Keywords: *Acute lymphoblastic leukemia, methotrexate, polymorphism*

Beuy Joob, Viroj Wiwanitkit[1,2,3,4]

Sanitation 1 Medical Academic Center, Bangkok, Thailand, [1]Department of Tropical Medicine, Hainan Medical University, Haikou, China, [2]Department of Medicine, Faculty of Medicine, University of Nis, Nis, Serbia, [3]Department of Biological Science, Joseph Ayobabalola University, Ilara-Mokin, Nigeria, [4]Department of Community Medicine, Dr. DY Patil Medical University, Pune, Maharashtra, India

Introduction

Acute lymphoblastic leukemia (ALL) is a common pediatric malignancy. Methotrexate is the widely used chemotherapy for ALL.[1,2] Appropriate therapeutic level of methotrexate is the important consideration in treatment.[1,2] The underlying genetic factors are proposed for a relationship with the serum methotrexate level.[3] Molecularly, solute carrier family 19, member 1 (*SLC19A1*) which corresponds as a miRNA-binding site for further regulation process that results in control of finalized serum methotrexate level is an important molecule in therapeutic concern.[4] The polymorphism (rs1051296) of SLC19A1 is proposed for its effect on serum methotrexate.[4] Wang *et al*. noted that "delayed elimination of methotrexate (C42 h >1 μmol/L) was less frequent in GG carriers than in GT and TT carriers."[4] To explain this observation, the authors hereby studied the interrelationship between SLC19A1 polymorphism and blood methotrexate level in the patients with ALL.

Materials and Methods

Here, the authors use a quantum chemistry analysis for explaining of this observation. Basically, quantum chemical modeling analysis was performed. The concept is the same as described in the previous study by Wiwanitkit.[5] Conceptually, the pharmacological action of the methotrexate requires basic biochemical reaction between drug and malignancy molecules. In each reaction, there will be a required reaction energy to complete the pharmacobiological process. Based on the basic clinical biochemistry, the two important determinants for the process are drug and malignancy molecule. For all patients, the drug molecule is in the same form, but the malignancy molecule is varied and dependent on the underlying genetic background, the polymorphism. This concept is used for writing a model to estimate the required reaction energy. For modeling of the chemical reaction, as an assumption, the required reaction energy for mRNA binding is first assigned to be "X" kCal/mol for one g of *SLC19A1*. Then, the variable due to the effect of polymorphism is assigned for further study. The variability in this modeling study is the change in substrate, *SLC19A1* due to different genotypes (GG, GT, and TT). Hence, "X" directly depends on the amount per mole of nucleotides and the different of "X" in each case is due to the difference of the amount of nucleotide at focused sites due to polymorphism. To start the mathematical modeling, the molecular weight of nucleotide at focused sites could be first derived by basic quantum chemical calculation. Determination of weight per mole of studied nucleotide parts is by basic quantum chemical technique as described in previous referenced publication.[5] At first, the calculation was done to find the amount per mole of nucleotide of the naïve type and

How to cite this article: Joob B, Wiwanitkit V. *SLC19A1* polymorphism and serum methotrexate in patients with acute lymphoblastic leukemia. Indian J Med Paediatr Oncol 2018;39:120-1.

Address for correspondence:
Dr. Beuy Joob,
Sanitation 1 Medical Academic Center, Bangkok Thailand.
E-mail: beuyjoob@hotmail.com

Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_6_16

Quick Response Code:

the amount per mole of nucleotide at focused site could be derived and further used as a primary template for modeling calculation for the specific values for mutated types. Then, the amount per mole of nucleotide at focused sites due to polymorphism can be further calculated by calculation of molecule weight change due to polymorphism assigned to the naïve type polymorphism in each mutated type.

Results

The required energy for binding in each genotype is calculated and is presented in Table 1. The amount per mole of nucleotide at focused sites is highest for GG type and lowest for TT type. The required energy per mole is also highest for GG type and lowest for TT type.

Discussion

The molecular change due to polymorphism is a natural underlying physiological factor that can affect the response to pharmacological action of any drug. In oncology, the effect of genetic polymorphism is of concern since it can result in failure of many anticancer drugs, especially for leukemia.[6] The alteration of the basic pharmacological reaction due to polymorphisms is of concern, and it is the topic for cancer therapy research. Quantum chemical analysis of the reaction is an important technique for patho-pharmacogenomics study. The good example is a previous report using this technique[5] for analysis of reaction between imatinib and Abl tyrosine kinase domain. The energy reaction which is affected by mutation is verified as an important explanation for the ineffectiveness of imatinib.

In this study, the authors focused the interest on the interrelationship between *SLC19A1* polymorphism and blood methotrexate level in ALL. The standard quantum chemistry analysis was used to assess the phenomenon. The studied polymorphism is the focused genetic background that is widely discussed for its effect on methotrexate dose in leukemia treatment.[4,7] In this study, it can be seen that the GG genotype requires the highest energy per mole which imply the least change in the formation of outcome. This is concordant with the report by Wang *et al*.[4] Based our prediction, the amount of serum methotrexate in TT genotype is 1.10 and 1.20 times more than GT and GG, respectively. This is also concordant with the observation by Wang *et al*.[4] that the amount of serum methotrexate in TT genotype is 1.21 and 1.31 times more than GT and GG, respectively.

Table 1: Predicted outcome concentration of product

Types	Amount per mole of nucleotide at focused sites (g)	Required energy per mole
GG	302.2552	302.5552X
GT	277.2394	277.2394X
TT	252.2266	252.2266X

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, *et al.* Childhood acute lymphoblastic leukemia: Progress through collaboration. J Clin Oncol 2015;33:2938-48.
2. Koh K. Current treatment of pediatric acute lymphoblastic leukemia. Rinsho Ketsueki 2014;55:2225-32.
3. Tasian SK, Loh ML, Hunger SP. Childhood acute lymphoblastic leukemia: Integrating genomics into therapy. Cancer 2015;121:3577-90.
4. Wang SM, Sun LL, Zeng WX, Wu WS, Zhang GL. Effects of a microRNA binding site polymorphism in SLC19A1 on methotrexate concentrations in Chinese children with acute lymphoblastic leukemia. Med Oncol 2014;31:62.
5. Wiwanitkit V. Analysis of binding energy activity of imatinib and Abl tyrosine kinase domain based on simple consideration for conformational change: An explanation for variation in imatinib effect in mutated type. Indian J Cancer 2009;46:335-6.
6. Dulucq S, Laverdière C, Sinnett D, Krajinovic M. Pharmacogenetic considerations for acute lymphoblastic leukemia therapies. Expert Opin Drug Metab Toxicol 2014;10:699-719.
7. Gutierrez-Camino A, Lopez-Lopez E, Garcia-Orad A. SLC19A1 hot spot for MTX plasma concentration. Med Oncol 2014;31:204.