Influence of Single-Nucleotide Polymorphisms on High-Dose Methotrexate Pharmacokinetics, Clinical Outcomes, and Adverse Effects in Patients With Acute Lymphoblastic Leukaemia in a North Indian Tertiary Care Hospital

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Introduction

Treatment of acute lymphoblastic leukemia (ALL) in adults is challenging with poor outcomes. we adopted a modified versions of BFM – 90 protocol to treat our AYA ALL patient. Routine TDM of plasma HDMTX levels has been strongly recommended to reduce the incidence of adverse events by leucovorin rescue.

The genetic association of HDMTX has been widely studied; However, conflicting results have limited its clinical usefulness. ALL prognosis and MTX effectiveness have been proven to be significantly affected by variations in single nucleotide polymorphisms (SNPs) of genes encoding MTX enzymes of metabolic pathways and transporters.

Aim

To evaluate the role of genetic polymorphism on high-dose methotrexate pharmacokinetics, adverse events, and clinical outcomes in patients with acute lymphoblastic leukemia.

Objectives

To correlate genetic polymorphism of MTHFR C677T, SLCO1B1 rs10841753, and SLCA119A 80 G>A with plasma methotrexate levels, clinical outcomes and Adverse events in ALL patients

Methods

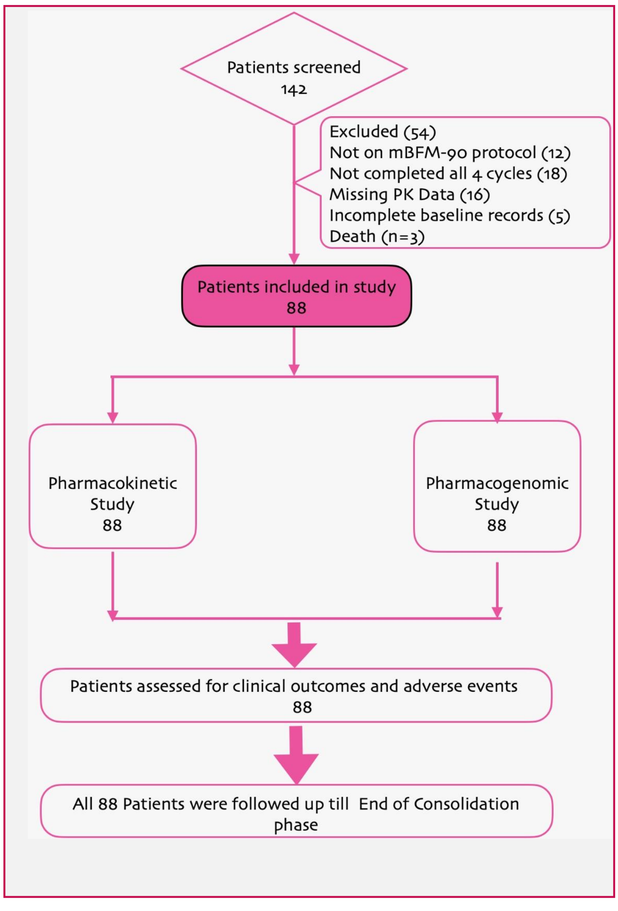


Figure 1 :Workflow of Study Patients

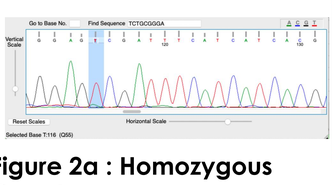


Figure 2a : Homozygous Genotype of MTHFR 677 TT.

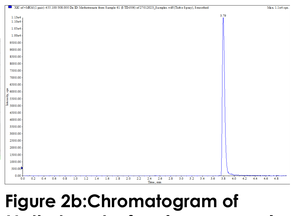


Figure 2b:Chromatogram of Methotrexate for plasma sample of study patient.

Results

Figure 4 : Plasma Methotrexate Level at 48 hours and 72 hours

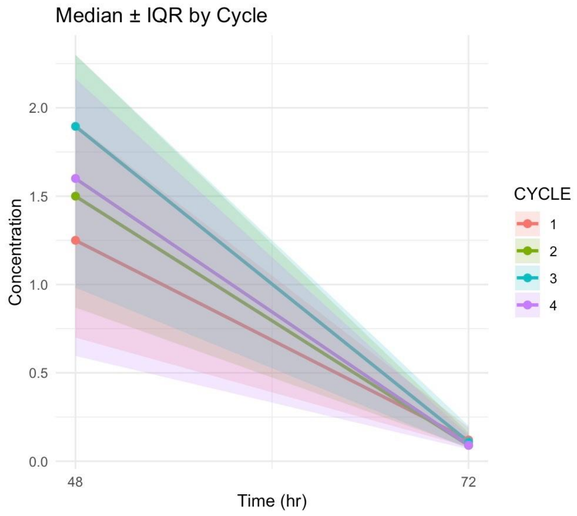


Figure 5 : Plasma Methotrexate Level at 48 hours with MTHFR allele Status

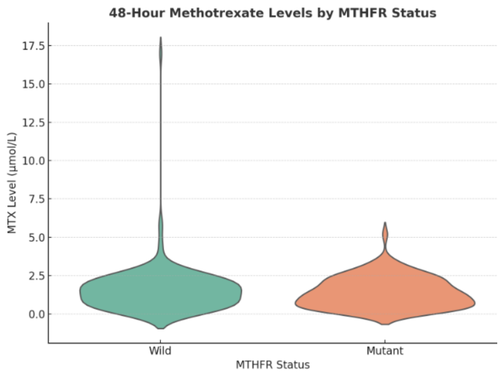
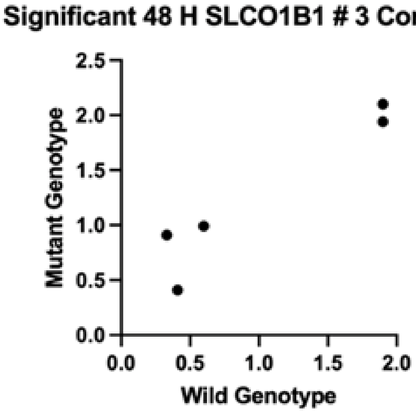


Figure 6 : Plasma Methotrexate Level at 48 hours with SLCO1B1



Summary

We have characterized Pharmacokinetics of HDMTX and influence of SNP on plasma MTX and clinical outcome and adverse effects.

Discussion

The association between selected SNP's and plasma methotrexate level at 48 hours with a cut-off value of greater than 1 micromolar/ L and less than 1 micromolar/L.

References

Carobolante F, Chiaretti S, Skert C, Bassan R. Practical guidance for the management of acute lymphoblastic leukemia in the adolescent and young adult population. Ther Adv Hematol. 2020 Feb 3;11:20.