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CHALLENGES IN USING PHARMACOMETRICS MODEL IN DOSING MERCAPTOPURINES IN LEUKEMIA

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ABSTRACT

Mercaptopurine (6-MP) is a key component of maintenance therapy for acute lymphoblastic leukemia, but optimizing its dose is challenging due to large differences between patients in how the drug is metabolized and how they respond. This review discusses the pharmacometric models used to support 6-MP dosing, with a focus on population pharmacokinetic (PopPK) approaches that describe the kinetics of its active metabolites—6-thioguanine nucleotides (6-TGNs) and 6-methylmercaptopurine nucleotides (6-mMPNs).The article outlines how 6-MP is processed through competing enzymatic pathways, chiefly involving thiopurine S-methyltransferase (TPMT) and NUDT15, producing metabolites that drive both therapeutic benefit and toxicity. PopPK models based on nonlinear mixed-effects methods have allowed researchers to estimate clearance parameters, explain inter-patient variability, and include patient-specific covariates such as age, weight, and genotype. Regression-based extensions of these models provide a more refined way to capture the drug's nonlinear kinetics and complex covariate-effect relationships.A major challenge emphasized in the review is the impact of TPMT and NUDT15 genetic polymorphisms, which differ widely across populations—especially in Asian and Indian cohorts—and strongly influence the risk of myelosuppression and hepatotoxicity. The difficulty of measuring intracellular 6-TGN concentrations, along with the long duration of maintenance therapy and ongoing changes in patient physiology, further hinders accurate dose individualization.The article concludes that building out pharmacogenomic testing capacity, developing population-specific pharmacometric models that reflect local allele frequencies, and integrating model-informed precision dosing (MIPD) with Bayesian updating are crucial steps toward achieving safer and more effective 6-MP therapy in the management of leukemia.

KEYWORDS: Pharmacometrics, pharmacokinetic-pharmacodynamic (PK/PD) modeling, population pharmacokinetics (PopPK), physiologically-based pharmacokinetic (PBPK) modeling, model-informed precision

ABBREVATION

PK – Pharmacokinetics, PD – Pharmacodynamics
PK/PD – Pharmacokinetic–pharmacodynamic
PopPK – Population pharmacokinetics
PBPK – Physiologically based pharmacokinetics
MIPD – Model-informed precision dosing
MLE – Maximum likelihood estimation
NONMEM – Nonlinear Mixed Effects Modeling (software)
NGS – Next-generation sequencing
PCR – Polymerase chain reaction
IIV – Inter-individual variability
FOCE – First-order conditional estimation
VPC – Visual predictive check
ME – Mean prediction error
RMSE – Root mean square prediction error
WRES – Weighted residuals
ALL – Acute lymphoblastic leukemia
AML – Acute myeloid leukemia
CML – Chronic myeloid leukemia
CLL – Chronic lymphocytic leukemia
NSCLC – Non-small-cell lung carcinoma
IBD – Inflammatory bowel disease
6-MP / 6MP – 6-mercaptopurine (mercaptopurine)

MTX – Methotrexate
6-TGN / 6TGN – 6-thioguanine nucleotides
6-TGTP – 6-thioguanosine triphosphate
6-dTGTP – Deoxy-6-thioguanosine triphosphate
TIMP – Thioinosine monophosphate
Me-TIMP – Methyl-thioinosine monophosphate
6-mMPN / 6-mMPNs – 6-methylmercaptopurine nucleotides
Ery-6TGN / E-TGN – Erythrocyte 6-thioguanine nucleotide
HGPRT – Hypoxanthine-guanine phosphoribosyltransferase
TPMT – Thiopurine S-methyltransferase
NUDT15 – Nudix hydrolase 15
ITPA – Inosine triphosphate pyrophosphatase
XO – Xanthine oxidase
NT5C2 – 5′-nucleotidase, cytosolic II
CPIC – Clinical Pharmacogenetics Implementation Consortium

INTRODUCTION

Pharmacometrics is a specialized field that focuses on the methodology and modeling of pharmacological and clinical dimensions, analyzing the interactions between xenobiotics and living organisms, which includes both beneficial and adverse effects.[1] It employs sophisticated models derived from biological, pharmacological, and physiological principles to quantitatively assess drug-case relationships, emphasizing population variability. Key components include systems pharmacology, pharmacokinetics, pharmacodynamics, and disease progression, with foundational models such as pharmacokinetic-pharmacodynamic (PK/PD) modeling.[2] This involves selecting and optimizing objective functions to fit statistical models to data, with maximum likelihood estimation (MLE) often used to determine parameters. Population PK (PopPK) models are empirical, incorporating theoretical pharmacological insights rather than specific empirical evidence, requiring careful validation dependent on the data used.[3,4,5,6] Various software packages, including NONMEM, Phoenix WinNonlin, Simcyp, and Monolix, facilitate pharmacometric analysis. PopPK modeling is inherently data-driven and focuses on the influence of covariates on pharmacokinetic parameters.[7,8] Additionally, physiologically-based pharmacokinetics (PBPK) modeling provides a complex, flow-based approach using detailed physiological knowledge to predict pharmacokinetics in various anatomical conditions, often validated against independent data sources to ensure accuracy.[9] These models can simulate drug behavior in artificial organ systems to tailor therapeutic approaches effectively.[10]

PHARMACOMETRICS MODELS IN ONCOLOGY

Pharmacometrics in oncology is mainly used by Model-informed precision dosing (MIPD), Population PK/PD and Disease Progression Models, and Biomarker Integration. Model-informed precision dosing aims to provide the optimal dose for each individual patient by leveraging prior knowledge embedded in mathematical population pharmacokinetic (popPK) models to inform dosing decisions[11] MIPD is only useful when there is substantial inter-individual variability in drug exposure with little intra-individual variability and a well-established (restricted) therapeutic window predictive of efficacy and/or effectiveness.[12] PopPK models are generally regarded as empirical models since they incorporate theoretical aspects, including those that are supported by the understanding of pharmacological parcels rather than by any particular substantiation. To validate the use of these tools the kind of data at hand, sufficient appreciation and evaluation are needed. The use of monoclonal antibodies and small-molecule tyrosine kinase inhibitors that target EGFR in colorectal malignancies and non-small-cell lung carcinoma (NSCLC) was made possible by this understanding of biomarkers.[13]

MECHANISM OF MERCAPTOPURINE

Acute lymphoblastic leukemia is managed and treated using the drug mercaptopurine. It belongs to the group of drugs called purine antagonists[14] Mercaptopurine is a prodrug of hypoxanthine, a purine analog that inhibits RNA and protein synthesis and acts as an antagonist to endogenous purines needed for DNA replication during the cell cycle's S-phase . For 6MP to become active and have antileukemic effects, it must be converted into 6-thioguanine nucleotides (6TGN).[15] The purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) in the liver, GI tract, and lymphocytes transforms the prodrug into thioguanine nucleotides 6TGN and thioinosine monophosphate (TIMP). Furthermore, 6-methylmercaptopurine, an inactive methylated base, is produced by a parallel pathway via thiopurine methyltransferase (TPMT). The methylated metabolite methyl-thioinosine monophosphate (Me-TIMP) significantly inhibits purine de novo production (DNA synthesis).[16] 6-thioguanine triphosphate (6-TGTP) inserts into RNA, while deoxy-6-thioguanine triphosphate (6-dTGTP) incorporates into DNA. In T-lymphocytes, 6-TGTP also binds to Rac1, inactivating the Vav-Rac1 signaling pathway. Additionally, this process stops Rac1 target genes such nuclear factor kappa beta (NF-kB) from activating, which causes activated T-lymphocytes to undergo apoptosis.[15] In this drug the two metabolised product is produce that are TPMT and NUDT15.

STANDARD PHARMACOMETRICS (DOSING) OF MERCAPTOPURINE IN LEUKEMIA

Leukemia has been defined as a primary or secondary process depending on the production of abnormal leukocytes. Depending on the rapidity of proliferation, they may be called acute or chronic, and based on cell origin, they are myeloid or lymphoid. Predominant subtypes include AML (Acute myeloid leukemia) and CML (chronic myeloid leukemia), involving the myeloid lineage; ALL (acute lymphoid leukemia); and CLL

(chronic lymphoid leukemia), involving the lymphoid chain.[17] Drugs are given to a wide range of patients and patient groups, from newborns to adults, with varying physiopathological diseases, stages of growth and maturation. Drug pharmacokinetics and dynamics in this setting must be connected to personal traits, i.e environmental (drug interactions, for instance) or constitutional (age, weight, genetics, etc.).[18] In adult ALL regimens, 6-MP dosages are usually 60 mg/m2/day during induction and consolidation and up to 75 mg/m2/day during maintenance. According to Guideline for 6-mercaptopurinedosing in adult acute lymphoblastic leukaemia based on TPMT and NUDT15 genotypes, starting doses for persons over 60 are usually lower. In order to maintain the neutrophil count between 0.75 and 1.5 x 109/l and the platelet count between 75 and 150 x 109/l, doses of 6-MP are increased in 25% dose increments at four weekly intervals (alternating with titration of oral methotrexate). 6-MP does not have a maximum dosage. 6-MP and methotrexate should be reduced by 50% if neutrophils are less than 0.75 x 109/l; if neutrophils are less than 0.5 x 109/l, both medications should be stopped and restarted at 100% if neutrophils are more than 0.75 x 109/l. To keep the platelet count between 75 and 150 x 109/l, similar modifications are made.[19] Adults with malignancies other than leukemia often tolerated 2.5 mg/kg for extended periods of time. The dosage was then increased in a few instances to 5 mg/kg each day.[20]

TOXICITY OF MERCAPTOPURINE LEUKOPENIA

Mercaptopurine may cause the leukopenia .Dose modifications based on toxicity are predicated on the idea that leukemic and normal cells are simultaneously impacted by individual differences in 6MP pharmacokinetics and pharmacodynamics.[21] The WBC levels reflect both treatment intensity and the child's natural WBC level, which varies both across and within age groups, and by ethnicity. Thus, patients with lower WBC levels during therapy also have low WBC after termination of therapy[22] Additionally, dose-intensified patients may be more susceptible to relapse if purine de novo synthesis is inhibited.[23]

THROMBOCYTOPENIA

Mercaptopurine may cause the thrombocytopenia. Thrombocytopenia is rarely a dose-limiting issue during 6MP/MTX maintenance therapy, although there is a substantial correlation between thrombocyte counts during and after stopping maintenance medication.[24]

HEPATOTIXICITY

6MP and MTX are hepatotoxic, and serum aminotransferase increases of two times or more are common. However, these elevations often return to normal a few weeks after maintenance medication is stopped.[25,26] Although there is frequently a slight increase in bilirubin or a decrease in coagulation factors, there appears to be little chance of severe and/or irreversible liver injury.[27,28,29] This may be due to either increased amounts of methylthioinosine monophosphate producing both liver toxicity and inhibition of purine de novo synthesis in leukemic cells also increasing hepatotoxicity.[30,31,23]

RELAPSE DURING MAINTENANCE THERAPY

Relapse during maintenance therapy has been linked to insufficient 6MP treatment intensity, as demonstrated by low Ery-6TGN levels.[32] According to two recent investigations, between 15% and 20% of both B-cell precursors had activating mutations in the NT5C2 gene, which is involved in nucleotide homeostasis[33] Patients with T-cell ALL21(T-cell acute lymphoblastic leukemia interleukin-21**)** who relapse while receiving 6MP maintenance treatment[34] When NT5C2(5′-nucleotidase, cytosolic II) mutations develop, patients relapse quickly, or after 6MP medication is stopped, the survival advantage for NT5C2-mutated clones at the expense of normal hematopoietic cells vanishes. Targeted deep sequencing may eventually enable routine screening for newly emerging clones with mutations that reduce the effectiveness of MTX (methotrexate) or thiopurines, allowing maintenance therapy to be modified to combat such resistance mechanisms.[23]

PHARMACOMETRIC ASSESSMENT MODELS FOR MERCAPTOPURINE DOSING OPTIMIZATION IN LEUKEMIA: FROM POPULATION PK MODELING TO MODEL VALIDATION

Population pharmacokinetic modelling (PopPk Model)

Population pharmacokinetic (PopPK) model is used in pharmacometrics of mercaptopurine in leukemia. Using a PopPK model, the pharmacokinetics of 6-MP active metabolites, 6-TGNs and 6-mMPNs, were ascertained by simultaneously analyzing concentrations from ALL individuals to provide estimations of the pharmacokinetic parameters. Extended least squares regression utilizing nonmem (version VI, level 1.1 with double precision) was utilized to model nonlinear mixed effects using the RBC concentration–time profiles of 6-TGNs and 6-mMPNs.[35] For the aim of developing the pharmacokinetic model, patients were randomly assigned to either an index group (n = 15) or a validation group (n = 4) to evaluate the generated model's predictive performance. Population mean parameters, interindividual variability (IIV) in these parameters, and residual variability between observed and anticipated metabolite concentrations were all estimated using the first-order conditional estimation (FOCE) approach with interaction. A one-compartment model with first-order absorption and elimination was used to characterize the concentration–time courses of 6-MP metabolites. The literature states that the model's absorption rate constant (ka) and bioavailability factor (F) were set at 1.3 h−1h and 22%, respectively. Clearance (CL) for 6-TGNs and 6-mMPNs as well as the fractional metabolic conversion

of 6-MP into 6-TGNs were the pharmacokinetic parameters calculated from this model.

The following differential equations were used to define the relationship between the parent medication and its metabolites:

$$\frac{dA(6-MP)_{Gut}}{dt} = -K_a \times F \times A(6-MP)_{Gut}$$

$$\frac{dA(6-MP)_{Central}}{dt} = K_a \times F \times A(6-MP)_{Gut} - K_{20} \times A(6-MP)_{Central}$$

$$\frac{dA(6-TGNs)_{Central}}{dt} = FM_3 \times K_{me} \times A(6-MP)_{Central} - CL_{6-TGNs} \times C(6-TGNs)_{Central}$$

$$\frac{dA(6-mMPNs)_{Central}}{dt} = FM_4 \times K_{me} \times A(6-MP)_{Central}$$
$$-CL_{6-mMPNs} \times C(6-mMPNs)_{Central}$$

Where kme is the metabolic transformation rate constant of the parent drug into either 6-TGNs or 6-MPNs, ka is the absorption rate constant of the parent drug, and k20 is the elimination rate constant of 6-MP (k20 = 0.53 h−1 based on literature. FMi is the fractional metabolic transformation into the metabolite I (6-TGNs are denoted by the number 3 and 6-mMPNs by the number 4, FM4 = 1–FM3), and A, C are the drug or metabolite amount or concentration at time t. k20 = kme + kother (kother is the elimination rate constant of bioavailable 6-MP transformed by other metabolic processes, kother = According to the literature, 0.22 × k20 = 0.1166 h−1.[36,37,38]

The individual's clearance deviations from the real (but unknown) population mean values were described using an exponential error model:

$$CL_i = TVCL \times e^{\eta_i CL}$$

where TVCL is the typical population estimate for CL and ηi, CL_i is the CL of the ith individual, and CL is a random variable that separates the parameter of the ith individual from the population mean values as predicted by the regression model. It is assumed to be normally distributed in the log domain with a geometric mean of zero and an Inline graphic variance. However, the remaining variability was best explained by the additive error model. This variability may result from assay error, model misspecification, non-adherence to medication, intra-individual variability in the pharmacokinetic parameters, or inaccurate timing of sample collection and dose administration.

$$C_{ij} = C_{pred,ij} + \varepsilon_{ij}$$

The residual error term, denoted by εij, is a random variable with zero mean and variance of σ2, whereas Cij is the measured and Cpred, ij is the model projected metabolite concentration of the ith person at the jth sampling period. A standard deviation (SD) was used to represent the amount of residual error or variability.[39] So basically this model is to evaluate the concentration of the of 6-TGNs and 6-mMPN, by this understanding the dosing of mercaptopurine in performed.

Regression model (advancement of PopPk model)

This is the advance model of PopPk model, In PopPk model 6-TGNs, and 6-mMPNs were first analysed using the BASE model, which did not include any patient factors. To find any possible correlation between CL and the covariates (variables that may influence the outcome), the conditional estimates of ηi, CL were derived from this BASE model and plotted against the following variables: age, gender, weight, body surface area (BSA), TPMT, (thiopurine S-methyltransferase) ITPA (inosine triphosphate pyrophosphatase), and XO (Xanthine oxidase genotypes). Each discovered covariate's impact on CL was evaluated separately by adding it to the BASE model (univariate analysis). For continuous variables, the regression relationship for CL was either linearly or nonlinearly modelled:

Proportional: $CL = \theta_{CL} \times (1 + \theta_{COV} \times COV)$

Power: $CL = \theta_{CL} \times COV^{\theta COV}$

Exponential: $\theta_{CL} \times e^{\theta COV \times COV}$

where COV is a general continuous covariate and θ_{CL} and θ_{COV} are the regression coefficients to be estimated by nonmem.(Nonlinear Mixed Effects Modeling)

Categorical covariates (1 or 0) were examined using a multiplicative model:

$$CL = \theta_{CL} + \theta_{COV} cov$$

Where θCOV is the fractional change when the covariate is present (COV = 1) and θCL is the population value when the covariate is absent (COV = 0). The impact of variables on FM3 (Experimental formulation) was examined using similar models. A likelihood ratio test was used to evaluate each model's increase in fit with the inclusion of a fixed effect variable (covariate). When a covariate is added, the objective function value (ΔOBJF) changes. This is a statistic that is proportional to minus twice the log-likelihood of the data{statistical method for comparing the goodness of fit of two nested models—a complex model ($L(\theta_0)$) and a simpler null model ($L(\theta_0)$)} and approximates a χ2 distribution with degrees of freedom equal to the difference in the number of

structural parameters (θs) between two models. For the inclusion of one fixed effect, a drop in the OBJF > 6.63 was deemed statistically significant (P < 0.01, 1 degree of freedom).

Each model with a significant effect was rated based on its ΔOBJF as compared to the BASE model as a consequence of the univariate analysis. After identifying the model with the highest ΔOBJF as the INTERMEDIATE model, multiple regression analysis with forward selection was carried out. Covariates were added to the INTERMEDIATE model one by one along the rank order determined by univariate analysis until all significant covariates were included and no more statistically significant reduction in OBJF was achieved (FULL model). The FINAL model was then produced via incremental, backward deletion of the FULL model. To keep the covariate in the FINAL model, the OBJF has to rise by ≥6.63 (P < 0.01, 1 degree of freedom).[39]

Model evaluation (Evaluation of assessment models)

The predictive utility of the population model was confirmed in the current study by internal validation utilising the data-splitting approach. The predictive performance of the model was assessed in terms of bias (mean prediction error) and precision (root mean square prediction error) by comparing the measured concentrations in the validation group with the corresponding predicted values by the population model using post hoc Bayesian forecasting. The structural and variance model parameters were fixed to the values calculated in the final population model in order to accomplish this.

The following formulas were used to calculate the mean prediction error (ME) and root mean square prediction error (RMSE).[40]

$$ME = \frac{1}{N}\sum_{i=1}^{N} p\, e_i$$

$$MSE = \frac{1}{N}\sum_{i=1}^{N} p\, e^2{}_i$$

$$RMSE = \sqrt{MSE}$$

The prediction error (pe_i) was calculated as:

$$pe_i = C_{obs} + C_{pred}$$

where Cobs and Cpred stand for the concentrations that were observed and anticipated, respectively.

To visually evaluate the differences between the model's predicted and observed metabolite concentrations in the validation group, weighted residuals (WRES) and measured metabolite concentrations were shown independently against the predicted concentrations.

A posterior visual predictive check was carried out by simulating from the final estimates and comparing the distribution of the observations with the simulated distribution in order to assess the performance of the final model, which was obtained by fitting the entire dataset (including the index and validation groups combined). Plotting the time history of the data and the prediction interval for the simulated values allowed for the demonstration of the model's suitability.[39]

CHALLENGE OF PHARMACOMETRICS OF MERCAPTOPURINE IN LEUKEMIA

The Challenge of pharmacometrics mercaptopurine in leukemia mainly occurs by Thiopurine methyltransferase (TPMT) and NUDT15 polymorphisms. It influences the toxicity and relapse of the leukemia. This metabolism differ from people to people based on their genomics. Identifying and integrating these genetic variants into the dosing model are more challenge till now. Researchers conducted a prospective research to assess the incidence of the genetic polymorphisms TPMT and NUDT15 in Indian IBD patients who had started using thiopurines and they estimated that how these polymorphisms relate to the incidence of cytopenia in our research sample.[41] These variant cause thiopurine intolerance in asian people's especially in indian population. Mercaptopurine is extensively metabolised, producing both active and inactive metabolites. Dose-response modelling is complicated by nonlinear kinetics and interpatient heterogeneity. The therapeutic effect mercaptopurine mainly depends on intracellular thioguanine nucleotide (TGN) levels which is difficult to measure, so the dosing calculation may end in error or false value. According to Gebhard, A., Lilienthal, P., Metzler, M. *et al.* article data's E-TGN observations made it possible to change each parameter separately, which led to patient-specific variations in E-TGN trajectories that affected the slope parameter's magnitude.[42] Mercaptopurine is mainly used as long term maintenance therapy for leukemia, For modelling dosing cumulative toxicity, adherence issues, and dynamic physiological changes must be predict accurately. This process may take over months or years. If misake happen on this relapse of leukemia will happen. The implementation of Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for thiopurine therapy (mercaptopurine) is critical in India because TPMT and NUDT15 variants cause cytopenia for Asian population. These establishment possess the molecular genetics infrastructure required for pre-treatment TPMT/NUDT15 genotyping, such as PCR or next-generation sequencing (NGS). Research has revealed that genetic profiles vary even within India, with certain areas exhibiting greater TPMT variations in addition to NUDT15, necessitating a customised strategy.

CONCLUSION

To overcome these challenges, expand the genetic diagnostic center in rural areas. Understand the importance of TPMT and NUDT15 variants in Indian population. Develop new popPK model for india reflect local allele frequencies. Integrate pharmacogenomics into national treatment protocol for standardize care because it shows the genetic information of the cancer. It will helps understand about patient and helpful for dosing model. regression model is used to handle non linear kinetic, multiple covariates and interactions. Use

of MIPD (Model-informed precision dosing) and updated Bayesian methods will helpful maintain the efficacy and toxicity of the mercaptopurine.

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