Ganciclovir dosing algorithms based on CKD-EPI and incorporating loading doses should be considered for treatment of CMV in alloHCT patients

Population Pharmacokinetics of Ganciclovir in Allogeneic Haematopoietic Stem Cell Transplant Patients

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Introduction

Treatment of cytomegalovirus (CMV) infection in allogeneic haematopoietic stem cell transplantation (alloHCT) patients with ganciclovir is complicated by toxicity and resistance

Therapeutic alternatives for CMV suppression are limited in this vulnerable patient group, and optimal dosing is critical to minimise toxicity and maximise efficacy

Aims

To develop a population pharmacokinetic model for ganciclovir in alloHCT patients with CMV viraemia or CMV disease and to perform simulations with this model to determine the optimal dosing regimens in this patient group.

Methods

Recruitment of 20 alloHCT patients requiring IV ganciclovir for CMV treatment

***n* = 10 with 1 sampling occasion**

***n* = 10 with 2 sampling occasions**

119 samples analysed using UPLC method

Population pharmacokinetic model

developed using Pmetrics version

1.9.7 software package for R

Monte Carlo Simulations (n=1000) performed for target attainment:

Induction: AUC_{24} 80 – 120

Maintenance: AUC_{24} 40 - 60

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Results

The ganciclovir concentration – time profile was best described with :

- **A 2-compartment model with linear elimination incorporating CL_{CR} estimated by the BSA-adjusted CKD-EPI equation**
- **Inclusion of between-occasion variability**
- **Independent estimation of ganciclovir CL for patients on CRRT**

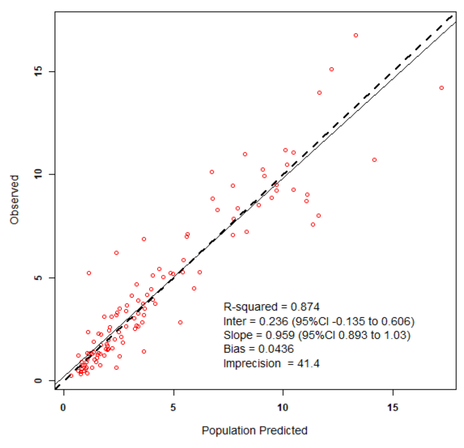
The final covariate model is displayed in the below equations:

Equation 1: $CL = TVCL \times (CL_{CR}/77)$

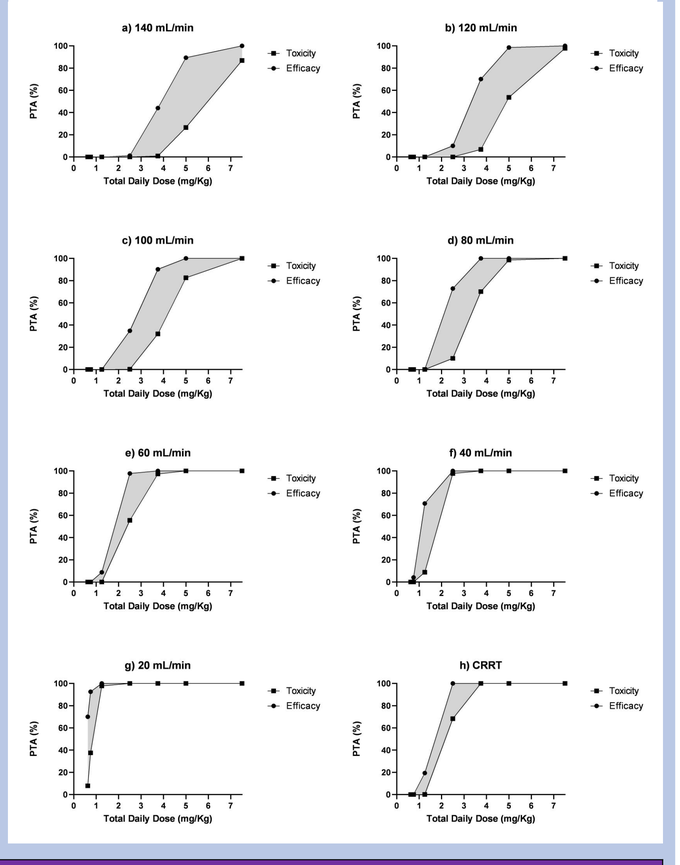
Equation 2: $CL = TVCL_{CRRT}$

TVCL is the typical value of ganciclovir clearance, $TVCL_{CRRT}$ is the typical value of ganciclovir clearance on CRRT, 77 is the overall median CL_{CR} value determined from patients in the study

Observed-versus-predicted goodness-of-fit plots for total ganciclovir concentration



Probability of target attainment of efficacy (AUC_{24} >80) and toxicity (AUC_{24} <120) on day 7 of ganciclovir induction



Suggested induction and maintenance dosing of ganciclovir based on creatinine clearance

CL_{CR}# (mL/min)	Suggested Induction Dosing regimen	Suggested Maintenance Dosing regimen
>120	7.5 mg/kg load then 5 mg/kg Q12H	5 mg/kg Q24H
101 - 120	7.5 mg/kg load then 3.75 mg/kg Q12H	3.75 mg/kg Q24H
81 - 100	5 mg/kg load then 3.75 mg/kg Q12H	3.75 mg/kg Q24H
61 - 80	5 mg/kg load then 2.5 mg/kg Q12H	2.5 mg/kg Q24H
41 - 60	6.25 mg/kg load then 3.75 mg/kg Q24H	2 mg/kg Q24H
31 - 40	5 mg/kg load then 2.5 mg/kg Q24H	1.25 mg/kg Q24H
21 - 30	3.75 mg/kg load then 1.5 mg/kg Q24H	0.75 mg/kg Q24H
≤20	3.75 mg/kg load then 1.25 mg/kg Q24H	0.625 mg/kg Q24H
CRRT	5 mg/kg load then 3.75 mg/kg Q24H	1.75 mg/kg Q24H

Abbreviations: Q12H; every 12 hours, Q24H; every 24 hours, CRRT; continuous renal replacement therapy
Calculated using body surface area adjusted Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

KEY FINDINGS

- **Loading doses of ganciclovir are recommended for the timely achievement of currently suggested target exposures**
- **CKD-EPI appears to be the renal function estimate best correlated with ganciclovir clearance, thus dosing calculations should be based on this rather than Cockcroft-Gault**
- **Further ganciclovir dose individualisation is required compared to the current product information recommendations due to its narrow therapeutic range and PK variability**

For more information

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