Ganciclovir Monitoring in a Cytomegalovirus Encephalitis Patient with End Stage Renal Failure: A Case Report.

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BACKGROUND :

Cytomegalovirus (CMV) encephalitis can be a serious and life-threatening condition in immunocompromised patients. The first line treatment of CMV encephalitis includes both intravenous ganciclovir and foscarnet[1]. Ganciclovir resistance is common when it is used as a single agent for CMV encephalitis treatment[1]. However, foscarnet is contraindicated and ganciclovir dose adjustments are required in patients with end stage renal failure (ESRF). Ganciclovir dosing in the treatment of CMV encephalitis in patients with ESRF is complicated in order to ensure adequate drug concentration and minimal concentration-related adverse effects such as myelosuppression and neurotoxicity[2].

OBJECTIVE:

Explore the use of therapeutic drug monitoring (TDM) to guide ganciclovir dose adjustments in a patient with CMV encephalitis and ESRF.

CLINICAL FEATURES:

A 31 year old Cambodian female (Patient KC) presented with new onset seizures, high fevers and acute kidney injury on admission. Cerebrospinal fluids (CSF) and plasma showed positive CMV results with signs of encephalitis observed on magnetic resonance imaging (MRI) of the brain.

A diagnosis of CMV encephalitis was made by the infectious diseases team.

Relevant Background:

- Stage 5 chronic kidney disease (CKD) secondary to systemic lupus erythematosus (on prednisolone and mycophenolate treatment).
- Renal function: 9mL/min(CKD-EPI), Creatinine clearance (CrCl)= 10mL/min (Cockcroft-Gault) with residual urine output.
- Candidate for peritoneal dialysis (PD) pending work up prior to this admission.
- Transverse myelitis and Brown-Sequard syndrome.
- No recent travel history, negative HIV serology.
- Normal full blood count except haemoglobin= 73g/L (secondary to CKD).
- Weight= 45.8kg, Height= 159cm.

Table 1. Pharmacokinetics of Ganciclovir

Dosing in Normal Renal Function:	**Induction:** IV Ganciclovir 5mg/kg BD[1] **Maintenance:** IV Ganciclovir 5mg/kg daily[1]
Absorption:	Not applicable
Distribution:	0.54- 0.87 L/kg[5]
Metabolism:	Not extensively metabolised[5]
Elimination:	Average half-life (normal renal function): 3.5 hrs[2] Predominantly renally cleared: ■ 90% is recovered unmetabolised in urine[5]. ■ 10-fold increase in elimination ½ life in patients with severe renal impairment[5].
CSF penetration:	24-70% depending on degree of brain inflammation[2]

CASE PROGRESSION AND OUTCOME:

Week 1

IV Ganciclovir 1.25mg/kg[5] (60mg) three times a week post HD commenced.

- Hemodialysis (HD) commenced.
- Plasma CMV viral load was 4025 copies/mL .
- Right eye CMV retinitis diagnosed on day 4 and intravitreal foscarnet and ganciclovir administered in right eye.

Week 2

Ganciclovir TDM performed.

- Patient reported hallucinations and headaches.
- Suspected possible disease progression and/or ganciclovir adverse effects.
- CMV viral load **decreased** to 1618 copies/ mL .

Week 3

Same dose of ganciclovir was continued.

- Resolution of hallucinations and headaches.

Week 4

Ganciclovir TDM results showed sub-therapeutic levels.

- **New diagnosis of left eye CMV retinitis.**
- Infectious diseases (ID) team was highly concerned of disease progression despite decreasing plasma viral load.
- Plasma CMV viral load was undetectable and **no ganciclovir resistance was identified.**

Week 5-11

Ganciclovir dose increased to 2mg/kg (90mg) three times a week post HD.

- A total of **11 weeks** of IV ganciclovir treatment.
- Discharged home with oral valganciclovir 150mg three times a week post HD.
- No myelosuppression was observed.
- No further neurological side effects were reported.

PHARMACIST INTERVENTIONS AND RESULTS:

1. Dosing Recommendation:

- Recommended ganciclovir dose adjustments according to patient's renal function (10-fold increase in elimination half life in ESRF patients[5]).
- Ensured dosing time charted as post HD as each intermittent HD session removes approximately 50-63% of ganciclovir[5].
- Provided recommendation on conversion from IV ganciclovir to valganciclovir (bioavailability of 66%[3]) and valganciclovir dose adjustments according to renal function. Therapeutic dose of valganciclovir was continued until review in ID clinic.

Table 2. Ganciclovir TDM results

Time of sample:	Levels:	Reference ranges:
Trough (prior to 6th dose)	0.2mg/L	0.25 - 1.2mg/L[4] (normal renal function) ***A surrogate target of trough ganciclovir plasma concentration > 0.3mg/L*** [3] *for optimal viral suppression*.
Peak level (60 minutes post the end of 6th infusion)	1mg/L	4.75 - 9.5mg/L[4] (normal renal function)

2. Therapeutic Drug Monitoring:

- **Suggested TDM to ensure adequate ganciclovir concentration for the treatment of encephalitis** (ganciclovir CSF penetration varies between 24-70%[2]) and prevent dose related side effects.
- **Trough levels were sampled prior to the 6th dose** (i.e. at steady state) and **peak level to be sampled 60 minutes post infusion** (after the 6th dose).
- **Recommended increasing dose** as low peak and trough ganciclovir levels (see. Table 2) with progression of left eye CMV retinitis with ongoing MRI abnormalities, suggested **treatment was subtherapeutic**. No ganciclovir resistance was detected.
- **Close monitoring on ganciclovir side effects** such as myelosuppression and neurotoxicity after increase in dose.
- **Prevented the use of foscarnet** (risk of permanent renal tubular necrosis) and the need for permanent HD which would negatively impact on patient's quality of life. Patient was planned for transitioning to PD post discharge.

DISCUSSION AND CONCLUSION:

There were two major challenges when performing TDM on ganciclovir:

1. Two weeks to process the results:
   a. Blood samples were transported interstate (in this instance QLD) for laboratory testing and
   b. Ganciclovir assays are performed only once a week.
2. The reference ranges for ganciclovir levels were derived from measuring plasma concentrations in patients with:
   a. Normal renal function at treatment doses[4] .
   b. Solid organ transplant recipients[3].

Additionally, the reference ranges have not been well researched in the guidance of dose adjustments for clinical efficacy or toxicity. An area under the curve (AUC) measurement may provide a more accurate measurement of ganciclovir exposure, but require appropriate monitoring software[3].

Dosing ganciclovir in end stage renal failure patients can be complex and TDM maybe required in critically ill patients. Further research and studies are required for guiding ganciclovir TDM and dose adjustments in ESRF patients.

References:

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