Management of Cytomegalovirus (CMV) Infection in Adult Haematology Patients

Introduction

Cytomegalovirus (CMV) reactivation and infection are major complications after allogeneic stem cell transplantation (STC) and are well-documented complications in patients with CLL receiving alemtuzumab (MabCampath), an anti-CD52 monoclonal antibody.

CMV reactivation typically occurs between weeks 3 and 8 of alemtuzumab treatment. However, routine CMV-specific prophylaxis is not recommended. Nevertheless, patients should be closely monitored for CMV reactivation using antigenaemia testing and/or PCR throughout treatment and follow-up periods[1].

Interpretation of CMV Viral Load Results

- The CMV viral load test is a quantitative PCR assay.
- CMV viral load testing is not yet subject to standardisation and results from different laboratories are not comparable. It is particularly important to be aware of whether the sample being tested is in plasma or whole blood when interpreting the results – see below. (The labs we currently use perform the assay on plasma samples**).
- Rapid increases in CMV viral load and high initial viral load are predictive of development of CMV disease.
- CMV "doubling time" is 24-48 hours; therefore, low level viral loads may rapidly become significant in immunocompromised patients.
- Viral load results are frequently reported in log copies/ml (e.g. 100copies/ml = 2 logs; 1000 copies/ml = 3 logs). As such, a 'significant' change in viral load is generally defined as > 0.5 log: changes of < 0.5 log may be the result of normal intra-assay variability.

Guide to Interpretation of CMV Load Copy Number

**CMV Load Copy No in plasma	CMV Load Copy No in whole blood	Interpretation/ Action	
CMV NOT detected	CMV NOT detected	No evidence for systemic* CMV infection: continue routine monitoring	
'CMV detected' but <300	'CMV detected' but <500	CMV DNA present below quantifiable level	Repeat CMV level in 24/48 hours
300 – 1,000	500 – 3000	Active CMV infection	Send repeat sample. Consider treatment if clinically indicated and/or viral load is rising
> 1,000 (preferably in 2 consecutive samples)	>3000	Active CMV infection	Send repeat sample. Commence pre-emptive treatment(do not wait for second result before commencing treatment)
***NB:**CMV end-organ disease (e.g. pneumonitis, colitis) is not ruled out by undetectable CMV viral load in blood			

Antiviral therapy

- The choice of antiviral therapy depends on the clinical setting and relative risk of toxicity (see table of drug treatment options below)
- Valganciclovir, the pro-drug of ganciclovir, greatly increases oral absorption, permitting therapy as an out-patient. Data has been published to confirm this in patients following allogeneic STC.[2]
- Please note: valganciclovir is not licensed for CMV treatment post STC or in patients with CLL. However there is good evidence to support its use in this setting.[3, 4]
- Discuss with haematology consultant and/or microbiology consultant before starting therapy
- Renal function needs to be monitored and dose needs to be adjusted accordingly, see below.

Continuation of alemtuzumab therapy

There are published guidelines[3] on the management of CMV which recommend that alemtuzumab therapy should be withheld only when patients have persistent, symptomatic CMV reactivation.
If a patient is CMV positive for two consecutive tests but remains asymptomatic, consideration should be given to administering oral valganciclovir while continuing alemtuzumab therapy.[1, 3] Discuss with haematology consultant.
Ongoing clinical assessment should be performed for symptomatic CMV infection during alemtuzumab treatment and for at least 2 months following completion of treatment.

Drug Treatment Options

<table>
<tr><th></th><th>Drug & Route of Administration</th><th>Clinical Setting[5]</th><th>Common side effects</th><th>Standard dose
(see below for dosing in renal impairment)</th><th>Duration</th></tr>
<tr><td>First line</td><td>Ganciclovir IV</td><td rowspan="2">Neutrophils > 1 x 10^9/l and platelets > 75 x 10^9/l</td><td rowspan="2">Neutropenia and thrombocyto-penia</td><td>5mg/kg IV bd
(If BMI ≥ 30, use IBW for calculating dose[6])
Infusion over 1 hour.</td><td rowspan="3">Minimum of 3 weeks.

Stop only after at least two consecutive samples in which CMV Load is ‘not detected’ or CMV DNA persistently dropped to very low levels with clinical improvement in patient’s condition.</td></tr>
<tr><td>After 1 week of inpatient therapy, falling CMV titres and pt clinically well to allow discharge</td><td>Valganciclovir PO</td><td>900mg PO bd</td></tr>
<tr><td>Second line Options</td><td colspan="4">Second line options need to be considered:
• if neutrophils < 1 x 10^9/l and/or platelets < 75 x 10^9/l
or
• for patients who do not respond to initial ganciclovir treatment i.e. with rising CMV titres after 2-3 weeks of ganciclovir therapy or with failure to eradicate CMV after 3 weeks of ganciclovir treatment. Please arrange for testing for ganciclovir resistance.

For resistant cases, always discuss with microbiology regarding the most appropriate option for 2nd line therapy.
Options include:
• Foscarnet IV
• Cidofovir IV
• Half dose ganciclovir with half dose Foscarnet

N.B. Foscarnet and Cidofovir are not stocked/formulary at all Trusts within the Alliance.</td></tr>
</table>

Ganciclovir supply out-of-hours

- Intravenous ganciclovir should be prepared aseptically.
- The Royal Surrey County Hospital (RSCH) pharmacy aseptic department keeps a supply of ready-made bags for out-of-hours use.
- The quantities and strengths kept are: 4 x 100mg, 4 x 150mg, 2 x 200mg, 2 x 250mg and 2 x 300mg.
- Please contact the RSCH on-call pharmacist via switchboard for any assistance regarding out-of-hours supply.
- The requesting hospital will be responsible for arranging transport to their site.

Dosing Information in Renal Impairment

CrCl (ml/min)	Induction dose of Ganciclovir (If BMI ≥ 30, use IBW for calculating dose[6])
≥70	5mg/kg every 12 hours
50 – 69	2.5mg/kg every 12 hours
25 – 49	2.5mg/kg every 24 hours
10 – 24	1.25mg/kg every 24 hours
< 10	1.25mg/kg every 24 hours after haemodialysis

CrCl (ml/min)	Induction dose of Valganciclovir
≥60	900mg twice daily
40 - 59	450mg twice daily
25 - 39	450mg once daily
10 - 24	450mg every 2 days
< 10	Not recommended

References

[1] Thomas Elter et al; Management of infections in patients with chronic lymphocytic leukemia treated with alemtuzumab; Ann Hematol (2009) 88: 121-132

[2] Herman Einsele et al, for the EBMT Working Group on Infectious Disease; Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation; Blood 2006; 107: 3002-3008

[3] Susan M. O'Brien et al; Updated guidelines on the Management of Cytomegalovirus Reactivation in patients with Chronic Lymphocytic Leukemia Treated with Alemtuzumab; Clinical Lymphoma & Myeloma Vol. 7, No 2 125-130, 2006

[4] H González et al; Successful oral valganciclovir treatment of cytomegalovirus infection during Campath-1H therapy; Leukemia (2005) 19, 478

[5] The Royal Marsden Haemato-Oncology Unit Guidelines May 2008

[6] Letter on file from Roche