DR. LAILA SUROUR SAIF AL YAZIDI (Orcid ID : 0000-0002-0459-3726)

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Management and prevention of cytomegalovirus infection in paediatric haematopoietic stem cell transplant (HSCT) recipients: a binational survey

Laila S Al Yazidi^{1, 2, 3} (FRACP), Richard Mitchell ^{2, 4} (FRACP), Pamela Palasanthiran^{1, 2} (FRACP, PhD), Tracey A O'Brien^{2, 4} (FRACP, MBA, LLM (Health, MBChB, BSc), Brendan McMullan^{1, 2, 5} (FRACP, FRCPA)

¹Immunology and Infectious Diseases department, Sydney Children's Hospital, Sydney, Australia;

²The School of Women's and Children's Health, University of New South Wales, Sydney, Australia;

³Sultan Qaboos University, College of Medicine, Muscat, Sultanate of Oman; ⁴Kids Cancer Centre, Sydney Children's Hospital, Sydney Australia; ⁵National Centre for Infections in Cancer,

University of Melbourne, Melbourne, Australia

Corresponding author:

Dr Brendan McMullan

Immunology and Infectious diseases department

Sydney Children's Hospital

High street, Randwick, NSW, Australia

E-mail: brendan.mcmullan@health.nsw.gov.au

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Dr Laila S. Al Yazidi conceptualized and designed the survey, distributed the survey to the selected centres, collected data, carried out the initial analyses and drafted the initial manuscript.

Dr Richard Mitchell revised the survey, helped with initial analysis and critically reviewed the manuscript

Dr Pamela Palasanthiran helped with data analysis and critical review of the manuscript.

Dr Tracey O'Brian helped with conceptualized the survey study and critically reviewed the manuscript.

Dr Brendan McMullan helped with survey revision, data analysis and writing the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

List of abbreviations:

CMV: Cytomegalovirus

HSCT: Hematopoietic stem cell transplantation

ID: Infectious Diseases

PCR: Polymerase chain reaction

DNA: Deoxyribonucleic acid

USA: United States of America

IV: Intravenous

TDM: Therapeutic drug monitoring

EBMT: European Society for Blood and Marrow Transplantation

Abstract

Background: Cytomegalovirus (CMV) infection is an important cause of morbidity and mortality among haematopoietic stem cell transplant (HSCT) recipients. Optimal strategies for prevention and management of CMV disease following haematopoietic stem cell transplantation remain uncertain.

Methods: We conducted an online survey of Australasian paediatric allogeneic HSCT centres on management and prevention of CMV disease in this patient group. We asked for one response from a representative of the HSCT team and one from a representative of the Infectious Diseases (ID) team at each centre.

Results: All Australasian paediatric HSCT centres responded to our survey. Management of CMV in pre-transplant setting was consistent between centres. All centres used a pre-emptive strategy to prevent CMV disease, guided by quantitative CMV PCR. In the post-transplant post engraftment setting, all centres recommended using ganciclovir (5mg/kg/dose twice daily) as a first-line therapy for CMV reactivation or disease, with treatment duration of 14 days, provided declining CMV quantitative PCR. There was substantial variability of practice between centres in post-transplant management of CMV reactivation, especially during the pre-engraftment phase. Similarly, there was lack of uniformity in indication, dosing and duration of maintenance therapy. Divergence was noted between responses from HSCT and ID physicians within centres.

Conclusions: This study identifies areas of uniformity and others of great variability in prevention and management strategies for CMV in paediatric HSCT. Data on CMV infection and management in HSCT patients should be routinely collected as part of prospective trials to inform guidelines and improve prevention and treatment of this important complication.

(250/250)

Introduction:

Despite advances in prevention and therapy of cytomegalovirus (CMV) disease, it remains an important cause of morbidity and mortality in persons undergoing haematopoietic stem cell transplantation (HSCT).¹ Cytomegalovirus (CMV) is an ubiquitous beta-herpes virus, which establishes lifelong latency following primary infection.^{2,3} In Australia, approximately 50% of the population are CMV seropositive by 15 years of age.⁴ CMV positivity is an important risk factor for disease following HSCT: without intervention, approximately half of HSCT CMV seropositive recipients will develop clinically significant infection, most commonly in the first 100 days post-transplant.² CMV disease in HSCT recipients can include pneumonia, retinitis, bone marrow suppression, colitis, hepatitis and encephalitis.² Management of CMV disease in HSCT recipients can include many clinician groups, including HSCT physicians and Infectious Diseases (ID) physicians. Prevention of CMV disease with either (a) universal prophylaxis or (b) a "pre-emptive strategy", frequent monitoring and early treatment of CMV viremia before manifestation of end organ CMV disease, has resulted in a reduction of CMV disease (but not viremia) from 20% to <2 % of patients undergoing HSCT.¹ The test most commonly used to monitor CMV viremia in these patients is CMV DNA polymerase chain reaction (PCR) assay. Use of the pre-emptive strategy has increased in recent decades and largely resulted in reduced toxicity and cost, compared to a prophylactic strategy, but has not been proven to be more effective.^{1,2,5} Intravenous ganciclovir and foscarnet are the most common anti-viral agents used in CMV management for this population, and each have potential side effects.¹ CMV management in HSCT patients is discussed in various guidelines. Two well-recognised guidelines are the European Conference on Infections in Leukaemia (ECIL) guidelines (2008) and the Updated International Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients (2009).^{6,7} Neither guideline includes specific recommendations on CMV management in children undergoing HSCT, however.^{6,7} A 2014 European international survey revealed striking differences among centres in CMV surveillance practices for prevention and management of CMV infection among paediatric HSCT recipients, but this survey had a <30% response rate, did not survey both HSCT and ID physicians at each centre, and did not ask questions about several practical issues, including turn-around times for CMV virological monitoring, use of therapeutic drug monitoring, or use of CMV-specific immunoglobulin.⁵ To our knowledge, there are no surveys of CMV infection management in

paediatric HSCT centres in Australasia and there are no national or widely accepted international guidelines. We therefore conducted this survey to assess the CMV infection prevention and management among Australasian paediatric HSCT centres.

Methods:

We surveyed all 6 paediatric allogeneic stem cell transplant centres in Australia and New Zealand, using a 38-item online questionnaire via SurveyMonkey™ (SurveyMonkey Inc. San Mateo, California, USA). There are approximately total of 200 transplants performed in these centres per year, with around 150 of these allogeneic transplants. The survey was developed by LA, based on literature review, with survey review by ID physician (BM) and HSCT physician (RM) to provide insight from each intended survey group. We then emailed a survey hyperlink to HSCT teams and Infectious Diseases teams at each centre, requesting one response by a representative from each team. The survey items included questions regarding pre-transplant management (part 1) and post-transplant management including virological monitoring, management strategies and antiviral treatment modalities (part 2). We also asked about the use of investigational therapies, such as CMV-specific immunoglobulin and cytotoxic anti-CMV T-cell therapy. The survey was initially emailed in June 2017. Reminders were sent after 2 weeks and one day before the closure day, July 2017. Results were calculated and as a proportion of 6 centres, unless otherwise specified below. HSCT team representatives' responses were considered to reflect day to day CMV management at individual centres. Unless otherwise indicated, responses for centres below are those given by HSCT team representatives. Responses from infectious diseases physicians were collected as we considered that ID physicians may provide advice to HSCT teams and be involved in formulation of guidelines for CMV management. Individual survey questions are available in Appendix 1. Only descriptive statistics were used in this study.

Ethics approval for this study was obtained from the Sydney Children's Hospital Network Human Research Ethics Committee.

Results:

Overview and CMV management strategy

HSCT and ID representatives from all 6 Australasian paediatric HSCT centres (12/12, 100% of those surveyed) responded within 6 weeks of the initial email and overall results for each centre are summarised in Table 1. As these comprise all centres performing HSCT in Australasia, we consider this sample representative of current practice. Five centres reported following local guidelines (two of these are guidelines designed for adult patients). No centres reported following national or international guidelines.

Post-transplant, all centres reported using a pre-emptive strategy to prevent CMV disease and all used quantitative PCR once or twice weekly to guide pre-emptive therapy. For the most part, infectious diseases physicians gave similar responses to HSCT physicians in their respective centres but differences were noted and these are specified below.

Testing

All centres used CMV PCR for viraemia monitoring. One centre reported using qualitative CMV PCR initially for screening followed by quantitative PCR if the virus is detected on qualitative PCR. One centre reported using pp65 antigenaemia testing in addition to CMV quantitative PCR. CMV quantitative PCR testing turnaround times ranged from one to four days (2 days on average). The threshold for starting pre-emptive therapy showed considerable variations among centres: 1000 – 10000 copies/ml. Five of the six centers reported starting pre-emptive therapy after one CMV PCR >1000 c/ml and the sixth centre starts if CMV PCR >10000 c/ml. All centres reported monitoring patients for CMV infection/reactivation until cessation of immunosuppression or immune reconstitution, but no centre defined immune reconstitution in their response. Viral resistance testing was performed by all centres if quantitative CMV PCR was increasing or not declining after 2 weeks of treatment.

Antiviral therapy

Of centres that routinely use antivirals prior to transplantation, ganciclovir was listed as the first line therapy by all 6 centres. All centres recommend using ganciclovir first-line for viraemia in the post-transplant, post-engraftment period, with a dose of 5mg/kg/dose twice daily and foscarnet as second-line therapy with a total dose of 180mg/kg/day in 2-3 divided doses. Centres recommended an initial treatment (induction) phase for duration of 14 days, provided declining CMV quantitative PCR was demonstrated. Antiviral choice for CMV reactivation or disease during the pre-engraftment period was not uniform: HSCT respondents at 3 centres recommended ganciclovir and 3 recommended foscarnet as first-line

therapy. In contrast, 5/6 ID specialists recommended ganciclovir for these, with one centre recommending either oral valganciclovir or IV foscarnet, depending on whether the patient can tolerate oral therapy. Four centres recommended routine ongoing maintenance therapy following an induction course for CMV reactivation. One did not recommend this routinely and one reported use dependent on patient immunosuppression. Switching to second line therapy was recommended if quantitative CMV PCR was increasing or not declining after 2 weeks of treatment, if the patient developed drug toxicity secondary to first line therapy or developed new symptoms suggestive of CMV end organ disease while on first line therapy. Therapeutic drug monitoring (TDM) was not routinely performed in any centre. One centre reported using TDM for patients receiving oral valganciclovir to confirm adequate drug levels.

End-organ disease

All centers recommended screening for CMV end-organ disease in those with CMV reactivation, based on the patient's clinical symptoms and signs, rather than routine investigations for all patients, but two centres specifically recommend routine eye examination for CMV retinitis. Recommended duration of treatment for CMV end-organ disease ranged between 2-4 weeks (average 3 weeks), with the potential for longer duration depending on clinical improvement and immunosuppressed status. All centres recommended ongoing maintenance therapy following end-organ disease, until immune reconstitution.

Adjunctive therapies

Only one HSCT centre routinely uses CMV-specific immunoglobulin (1.5 million units weekly) for HSCT recipients with CMV reactivation or CMV end-organ disease in addition to antiviral therapy. One other centre considers use of CMV-specific immunoglobulin for patients on reduced ganciclovir dosing in context of severe renal impairment. Responses for this question were received from 6/6 HSCT representatives, but only one infectious diseases respondent, who reported that CMV-specific immunoglobulin was recommended at their centre for patients with CMV pneumonitis. Four centres reported having used cytotoxic anti-CMV T-cell therapy as second-line or salvage therapy (3/4) or to prevent or treat CMV reactivation post HSCT (1/4). Three of the four infectious diseases team members at those centres were aware of use of CMV T-cell therapy in their centre as salvage therapy.

Discussion:

This is the first survey on CMV management in paediatric allogeneic HSCT in Australia and New Zealand, and the first worldwide to explicitly survey both HSCT and ID physicians at each centre. These Australasian centres surveyed uniformly use a pre-emptive strategy to prevent CMV disease, use quantitative CMV PCR for monitoring and guidance of treatment, and similar strategies for treatment for CMV reactivation and disease in the post-engraftment period. We found variability, however, regarding maintenance therapy, and in the management of CMV reactivation/disease in the pre-engraftment period.

In terms of testing, quantitative CMV PCR has now largely replaced the pp65 antigenemia in all of the Australasian paediatric HSCT centres to guide pre-emptive therapy but there is 10-fold variation as to the threshold to start pre-emptive therapy (1000 – 10 000 copies/ml). In addition, though not discussed in this survey, methods of sampling, DNA extraction and PCR assays, as well as turnaround times are not uniform and contribute further to variation. Results were reported in terms of copies/mL as reporting in IU/mL had not been adopted as standard in Australasian laboratories at the time of the survey.

There was significant variability in pre-engraftment antiviral therapy. This may be due to concern about graft failure with ganciclovir use in the 50% of the HSCT centres reporting using foscarnet as first line therapy, in contrast to the ID physicians surveyed, who largely recommended ganciclovir for this group.² The even split among HSCT physicians and divergence from ID physicians highlights a need for evidence to support optimal antiviral for these patients. The question also revealed a broader issue of the discrepancy between some responses of ID and HSCT physicians in this survey. We originally planned to survey ID physicians as well as HSCT physicians as we considered they would likely provide advice to HSCT teams and surmised perhaps they would be able to provide information on local practice even if we received no response from the respective HSCT physician at that centre. In fact, we received responses from all physicians surveyed and found an unexpected divergence between ID and HSCT physicians in understanding of local practice and recommendations. These health care provider groups have different perspectives, different expertise and are involved with HSCT patients unevenly, and divergent responses noted here suggests that efforts to improve both communication and collaboration between these groups are needed. Development and training of transplant-specific paediatric ID subspecialists

working at institutional, national and/or professional society levels may be useful to inform practice and bridge the gap.

We found only one other survey on CMV in children undergoing HSCT from the European Group for blood and marrow transplantation (EBMT).⁵ The authors reported all a 28.5% response rate, 56/196 participant centres responded, and all used a pre-emptive strategy for CMV disease prevention, with 55 using ganciclovir as first line therapy as part of a pre-emptive strategy, but only 22 centres using ganciclovir pre-engraftment.⁵ Twenty-one centres reported also using a prophylactic strategy, though it is unclear for which patient groups. Maintenance therapy was also widely given but highly variable in both the EBMT survey, as in our study, regarding indications and dosing. This variation is likely due to limited evidence to support particular strategies, and thus is a priority for further research and guideline development. CMV-specific immunoglobulin, used historically, was used routinely by only one centre surveyed in our study, and not mentioned in the EBMT survey.

No centres reported following national or international paediatric guidelines. These exist, as we have noted^{6,7} but are not paediatric-specific. It is unclear whether participants are aware of these guidelines or have used these to adapt local guidelines from the data in this survey. This point suggests that if consensus guidelines are to be developed, they must specifically address paediatric practice and have a plan for dissemination and implementation to be effective. Ultimately, it is likely that data comparing strategies and outcomes in this patient group are needed to provide a basis for development of such guidelines.

Limitations of our study include its small size: as there are only 6 centres in total managing HSCT in children in Australia and New Zealand, this is necessarily a small sample, and results may not be generalizable to other centres outside Australasia. In addition, the team member surveyed at each centre may not necessarily represent practice in that centre. There were some incomplete responses from participants, though these were uncommon, and the overall survey response rate was unusually high at 100%. We found that genotypic antiviral resistance testing is able to be accessed in all centres, though we received no information from respondents on turnaround times for this test, or the specific assay/targets used. We surveyed both HSCT and Infectious Diseases physicians at each centre with the same questions and for the most part answers were similar, but HSCT responses were more complete and likely describe actual day to day practice in centres. The redundancy built into our sampling may have been more useful had we had less than 100% responses. We may

have benefited from asking Infectious Diseases Physicians different specific questions focussed on guidelines, consultation and laboratory testing and liaison. Although we acknowledge it would be preferable to state viral load results in terms of IU/mL to facilitate comparisons, in practice our laboratories reported these results in terms of copies/mL and this informed our survey.

Conclusions: There is uniformity in CMV management in some areas among paediatric HSCT centres in Australasia but other areas of practice that remain diverse, suggesting unnecessary variation which could be reduced with better evidence to inform practice and develop consensus guidelines. Ideally, consensus guidelines including recommendations for viral monitoring for pre-emptive therapy, choice of agent for pre-engraftment therapy and dose and duration of maintenance therapy should be developed, but this will require evidence to inform them.

Future Direction: The next steps must involve HSCT centres and networks reviewing current practice, including areas of diversity against best current evidence. Where this evidence is lacking, further studies should be performed on whether there are attributable differences in outcome between different strategies used. Some of these studies may need to be pursued retrospectively, and some prospectively but these are needed to inform development of guidelines. Providing this evidence to the international community will advance understanding of CMV infection in this vulnerable group, and ultimately improve patient outcomes.

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Appendix:

Survey questions:

1- Where do you work?

- a) Queensland
- b) Victoria
- c) Western Australia
- d) NSW
- e) South Australia
- f) New Zealand

2- Please select your subspecialty:

- a) Infectious diseases
- b) Haematology/oncology

3- Does your facility follow local CMV management guidelines or other (e.g. published) guidelines for management of CMV infection in allogeneic Haematopoietic Stem Cell transplantation (HSCT) recipients?

- a) local guidelines
- b) no guidelines
- c) other guidelines - please specify (comment box)

Pre-transplant management:

4- Does discordant CMV sero-status between donor and recipient affect your practice in CMV management?

- No
- Yes (please specify how)

5- What is your first line choice antiviral therapy for CMV eradication therapy prior to transplant?

- High dose IV aciclovir
- IV Ganciclovir
- Oral Valganciclovir
- IV Foscarnet
- IV Cidofovir
- Other (please specify)

Post-transplant management:

Monitoring:

1- How long does it take for CMV monitoring results to come back at your centre?

- a. (please specify duration in whole days)

2- If you use both strategies but prophylactic versus pre-emptive strategy depends on patient/graft factors, which of these determine your practice:

- a. Non-malignant transplant – use prophylactic strategy
- b. Use of Almetuzumab– use prophylactic strategy
- c. Graft type (please specify all)

3- Which strategy do you follow in your centre for allogeneic transplant patients to prevent CMV disease post-transplant?

- Prophylactic strategy – GO TO QUESTION 4
- Pre-emptive strategy – GO TO QUESTION 8
- Both-GO TO QUESTION 4

Prophylactic Therapy

4- For prophylactic strategy, which test do you use for CMV monitoring: (choose all that apply)

- None
- Quantitative CMV PCR (viral load or copies/mL)
- Qualitative CMV PCR (CMV detected/not detected)
- pp65 antigenaemia
- Other (please specify)

5- How often do you perform the above testing?

- No testing
- Twice a week

- Once a week
- Once fortnightly
- Other (please specify)

6- When do you stop CMV monitoring in your HSCT patients?

- 100 days post-transplantation
- At discontinuation of immunosuppressive medications
- Negative surveillance tests for one month
- No monitoring done routinely
- Other (please specify)

7- If you use the prophylactic strategy - What is the recommended duration of prophylactic therapy at your centre?

- 100 days post-transplantation
- At discontinuation of immunosuppressive medications
- Negative surveillance tests for one month
- Other (please specify)

IF YOU DO NOT USE PRE-EMPTIVE STRATEGY, GO TO QUESTION 13

Pre-Emptive Therapy

8- For pre-emptive strategy, which test do you use for CMV monitoring: (choose all that apply)

- Quantitative CMV PCR
- Qualitative CMV PCR
- pp65 antigenaemia
- Other (please specify)

9- If you use quantitative CMV PCR, at what threshold do you start pre-emptive antiviral therapy at your centre?

- >500 copies/mL
- >1000 copies/mL
- >5000 copies/mL
- CMV detected (any level)
- Other (please specify)
- Not applicable

10- If you use CMV pp65 antigenemia, at what threshold do you start pre-emptive antiviral therapy at your centre?

- > 5 copies/ml
- > 10 copies /ml
- > 100 copies/ml
- Any positive results
- Other (please specify)
- Not applicable

11- After how many positive results (above your therapy threshold) do you start the treatment?

- One
- Two
- Other (please specify)

12- When do you stop CMV monitoring in your HSCT patients?

- 100 days post-transplantation
- At discontinuation of immunosuppressive medications
- Negative surveillance tests for one month
- No monitoring done routinely
- Other (please specify)

Therapy for CMV viraemia or disease:

13- What is your first line choice antiviral therapy during CMV reactivation post-transplant pre-engraftment?

- High dose IV aciclovir
- IV Ganciclovir
- Oral Valganciclovir
- IV Foscarnet
- IV Cidofovir

- Other (please specify)

14- What is your second line choice antiviral therapy during CMV reactivation post-transplant pre-engraftment?

- High dose IV aciclovir
- IV Ganciclovir
- Oral Valganciclovir
- IV Foscarnet
- IV Cidofovir
- Other (please specify)

15- What is your first line choice antiviral therapy during CMV reactivation post-transplant and post-engraftment?

- High dose aciclovir
- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir
- Other (please specify)

16- What is your second line choice antiviral therapy during CMV reactivation post-transplant and post-engraftment?

- High dose aciclovir
- Ganciclovir

- Valganciclovir
- Foscarnet
- Cidofovir
- Other (please specify)

17- In the event of reactivation of CMV disease if patient is on CMV prophylaxis, what CMV therapy do you use?

- Same as CMV prophylaxis but at treatment doses
- Swap to another CMV antiviral (second line CMV agent)
- Other (free text)

18- Please specify the dose and frequency of antiviral agent you chose above, used for first and second line ?treatment? therapy. (free text)

19- What is the recommended duration of treatment for CMV reactivation (viraemia only, without suspected end-organ disease) at your centre:

- 1 week, provided declining CMV PCR
- 2 weeks, provided declining CMV PCR
- 3 weeks
- Other (please specify)

20- Do you recommend ongoing antiviral (maintenance) therapy following a treatment course for CMV reactivation, viraemia only (If so, please specify the duration below)

- No
- Yes (please specify duration)

21- What are your criteria for stopping maintenance therapy following CMV reactivation, viraemia only. (free text).

22- When do you recommend screening/testing for CMV end-organ disease and what testing do you recommend? (free text)

23- What is the recommended duration of treatment for CMV end-organ disease at your centre: (please specify according to site of infection)

- CMV pneumonitis
- CMV encephalitis
- CMV colitis
- CMV myocarditis
- CMV retinitis

24- Do you recommend ongoing (maintenance) antiviral therapy following a treatment course for CMV end-organ disease (If so, please specify the duration below)

- No
- Yes
- Duration: (please specify)

25- What are your criteria for stopping maintenance therapy following CMV end-organ disease? (free text).

26- Do you recommend Therapeutic Drug Monitoring (TDM) of CMV antiviral therapy (E.g. ganciclovir levels)?

- Yes, routinely
- No
- If CMV quantitative PCR is not declining after 2 weeks of treatment dose.
- Other (please specify)

27- When do you test for CMV antiviral resistance? (Choose all that apply)

- If CMV quantitative PCR viral load is not declining after 2 weeks of treatment dose
- If CMV PCR viral load is increasing after 2 weeks of treatment
- If patients develop symptoms suggesting CMV end-organ disease despite first line therapy
- Other (please specify)

28- When do you switch to the second line therapy? (Choose all that apply)

- If CMV quantitative PCR viral load is not declining after 2 weeks of treatment dose
- If CMV PCR viral load is increasing after 2 weeks of treatment
- If the patient develops symptoms suggesting CMV end-organ disease despite 1st line therapy
- If the patient develops toxicity on first line therapy

- Other (please specify)

29- Do you use CMV Immunoglobulin at your centre? (You may select more than one answer)

- Yes, as part of prophylaxis for all patients
- Yes, as part of therapy for all patients
- Yes, as part of prophylaxis for some patients
- Yes as part of therapy for some patients
- No
- (please specify indications if “some patients” selected)

30- If you use the CMV immunoglobulin, please specify the dose, frequency and total duration. (Free text)

31- Have you used CMV-specific cytotoxic T-cell therapy at your centre?

- a. Yes
- b. No, not available
- c. No, has not been required
- d. Other

32- What is the role of CMV-specific cytotoxic T cell therapy, in your opinion? (free text)

33- Please list any other comments below (comment box)

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Table 1: summary of CMV management practice among the six Australasian paediatric HSCT centres

	Hospitals					
	A	B	C	D	E	F
Presence of local guideline	Y	Y	No	Y	Y	Y
Pre-transplant use of ganciclovir for CMV sero-positive children	Yes	Yes	Yes	Yes	Yes	Yes
Use pre-emptive strategy	Yes	Yes	Yes	Yes	Yes	Yes
Viral load turnaround time	2 days	2 days for qualitative and quantitative test can be done once weekly	1-4 days	2 days	2-3 days	2-4 days
Viral monitoring	quantitative PCR	qualitative PCR, if positive perform quantitative PCR	quantitative PCR	quantitative PCR	quantitative PCR	quantitative PCR
CMV PCR threshold for starting pre-emptive therapy	>1000 c/ml, one reading	>1000 c/ml (3 logs), one reading	>1000c/ml, one reading	2 readings of significant CMV PCR load, significant load has not been specified	> 10000 c/ml, 2 readings	>1000c/ml, one reading
1 st line antiviral pre-engraftment	Foscarnet	Ganciclovir	Foscarnet	Foscarnet	Ganciclovir	Ganciclovir
2 nd line anti-viral pre-engraftment	Cidofovir	Foscarnet	Ganciclovir	Ganciclovir	Foscarnet	Foscarnet
1 st line antiviral post-	Ganciclovir	Ganciclovir	Ganciclovir	Ganciclovir	Ganciclovir	Ganciclovir

engraftment						
2 nd line antiviral post-engraftment	Foscarnet	Foscarnet	Foscarnet	Foscarnet	Foscarnet	Foscarnet
Treatment dose of ganciclovir	5mg/kg/dose 12 hrly	5mg/kg/dose 12 hrly	5mg/kg/dose 12 hrly	5mg/kg/dose 12 hrly	5mg/kg/dose 12 hrly	5mg/kg/dose 12 hrly
Treatment dose of foscarnet	Not given	90mg/kg/dose 12 hrly	60mg/kg/dose 8 hrly	Not given	60mg/kg/dose 8 hrly	90mg/kg/dose 12 hrly
Duration of treatment of CMV reactivation	2 weeks provided declining CMV PCR	2 weeks provided declining CMV PCR	2 weeks provided declining CMV PCR	2 weeks provided declining CMV PCR	2 weeks provided declining CMV PCR	2 weeks provided declining CMV PCR
Use of maintenance therapy post-CMV reactivation	Yes	No	Yes	Sometimes based on immunosuppression	Yes	Yes
TDM	Not routine	No	Yes (routinely)	No	No	No
CMV IVIG	All CMV reactivations and end-organ disease	No	No	No	Part of prophylaxis in patients getting compromised ganciclovir dose secondary to severe renal toxicity	No
CMV specific cytotoxic T cell therapy	Second line therapy when available	2 nd line therapy for CMV disease	-	-	An effective strategy in preventing and treating CMV reactivation post HSCT	Salvage or second-line therapy

CMV: cytomegalovirus virus, c/ml: copy/milliliter, hrly: hourly, TDM: therapeutic drug monitoring, IVIG: intravenous immunoglobulins

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Author/s:

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