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Title

Effective CMV prophylaxis with High Dose Valaciclovir in Allogeneic Hematopoietic Stem Cell Recipients at High Risk of CMV Infection

Running Title

High Dose Valaciclovir as CMV Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplantation

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Conflicts of Interest

Dr Genevieve Douglas received honoraria from Roche

Dr Michelle Yong received honoraria and participated in advisory boards for Merck

Assoc Prof Joe Sasadeusz received research grants from Shire, participated on advisory board for Merck

Prof Monica Slavin received research grants from Merck, participated on advisory board for Merch and Takeda

Dr Lynette Chee received honoraria from Novartis, participated in advisory boards for Novartis and Otsuka

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Tweet: High dose valaciclovir prophylaxis reduces and delays CMV infections in high-risk allogeneic hematopoietic stem cell transplant recipients, reducing early requirement for pre-emptive CMV therapy.

Key Words

CMV, Valaciclovir, Prophylaxis, Bone Marrow Transplant

Structured abstract

Background

Cytomegalovirus (CMV) infection increases mortality and morbidity following allogeneic hematopoietic stem cell transplantation (alloHSCT). Universal antiviral prophylaxis with letermovir is effective, but unsubsidised in Australia. Valaciclovir demonstrates anti-CMV activity in high doses, but few current real-world studies explore its use as primary prophylaxis in high-risk patients post-alloHSCT.

Methods

We performed a retrospective analysis of alloHSCT recipients at high risk of clinically significant CMV infection (cs-CMVi), defined as plasma CMV DNA viral load of >400 IU/mL requiring pre-emptive therapy, or CMV disease. High risk recipients were CMV seropositive, and underwent T-cell depleted, haploidentical or umbilical cord stem cell transplants. Consecutive patients transplanted from July 2018–January 2020, treated with valaciclovir 2g TDS from day +7 to +100 (HD-VALA) were compared to a historical cohort (July 2017 - June 2018) who only received pre-emptive CMV therapy, and standard valaciclovir (SD-VALA) for varicella/herpes prophylaxis. We compared incidence of and time to cs-CMVi.

Results

In the SD-VALA cohort, (n=27, median CMV follow-up duration 259 days), 23/27 (85%) developed cs-CMVi at a median of 39 days. For the HD-VALA cohort, (n=35, median CMV follow-up duration 216 days), 19/35 (54%) developed cs-CMVi, at a median of 68 days. Time to cs-CMVi was significantly

longer in HD-VALA cohort (p<0.0001). On multivariate analysis, HD VALA reduced the risk of cs-CMVi (HR 0.32, p=0.0005).

Conclusions

In alloHSCT recipients at high-risk for cs-CMVi, HD-VALA resulted in lower cumulative reactivation, and delayed reactivation, reducing requirement for pre-emptive CMV therapy in the early post-engraftment period.

Introduction

Cytomegalovirus (CMV) infection increases non-relapse mortality following allogeneic hematopoietic stem cell transplantation (alloHSCT)[1-9]. Pre-emptive antiviral therapy is a well-established strategy, reducing the incidence of CMV disease[3,5,9,10]; however the toxicity of effective antivirals limits their tolerability in the fragile early post-engraftment period [5,9,11-14]. Universal prophylaxis using letermovir in CMV seropositive recipients is effective and well-tolerated[15], but is not subsidised in Australia, rendering it inaccessible to many alloHSCT recipients.

Patients with CMV infection post-alloHSCT predominantly have reactivation of latent virus. Risk factors include recipient seropositivity, umbilical cord blood (UCB) or haploidentical transplant, T-cell depletion, graft-versus-host disease (GVHD) and delayed T-cell recovery[1,4,16-18]. Aciclovir was the first antiviral shown in a randomised study to prevent CMV reactivation following alloHSCT, reducing CMV infection, and improving survival[19]. Valaciclovir (an orally bioavailable pro-drug of aciclovir) reduced CMV infection rates in 2 prospective randomised trials[20,21]. Retrospective studies in UCB and haploidentical alloHSCT suggest high dose valaciclovir (HD-VALA) prophylaxis leads to improved CMV-related outcomes[22,23], although they comprised cohorts with additional pre-transplant antiviral treatment, potentially confounding the effect of HD-VALA monotherapy[22].

We aimed to evaluate real-world efficacy and tolerability of HD-VALA as primary CMV prophylaxis in high-risk patients undergoing alloHSCT.

Methods

We performed a single-centre, retrospective analysis of alloHSCT recipients at high CMV risk, at the Royal Melbourne Hospital, Melbourne, Australia (Melbourne Health Human Research and Ethics Committee (HREC/17/MH/397). We defined high CMV risk as recipient CMV seropositivity and undergoing T-cell depletion, haploidentical or umbilical cord stem cell alloHSCT.

We performed twice-weekly quantitative plasma CMV DNA monitoring to ≥Day+100. Monitoring continued whilst patients remained on immunosuppression, if GVHD was present or if cs-CMVi occurred (Abbott Realtime CMV assay, reported in IU/ml, lower detection limit of 31 IU/ml). We defined cs-CMVi as plasma CMV DNA viral load of >400 IU/mL, or CMV disease, at which point CMV-specific antiviral therapy was initiated.

We compared cs-CMVi rates and time to reach cs-CMVi between:

- Cohort 1 **(SD-VALA control cohort)**: alloHSCT between July 2017 and June 2018, managed with pre-emptive CMV therapy. Valaciclovir (500mg BD until engraftment followed by 500mg daily), was commenced at conditioning commencement and continued for ≥12 months post-alloHSCT, for varicella and herpes simplex prophylaxis.
- Cohort 2 **(HD-VALA cohort):** alloHSCT between July 2018 and January 2020, given primary CMV prophylaxis with HD-VALA (2g TDS, or renally adjusted equivalent) from day +7 to ≥day +100 post-alloHSCT. Extension beyond D+100 occurred in 5 cases, due to ongoing need for immunosuppression and/or ongoing low-level detectable CMV. All patients commenced SD-VALA after HD-VALA cessation.

HD-VALA was renally adjusted if glomerular filtration rate (GFR) was 30-50mL/min to 2g BD, some clinicians opted for 1g TDS (n=5). HD-VALA was ceased if GFR deteriorated below 30mL/min. Some patients received IV aciclovir initially, due to oral mucositis or poor oral intake. Equivalent IV aciclovir dosing was 500mg/m^2 TDS, and patients were transitioned to oral HD-VALA once able to tolerate it.

Statistical analyses were performed in R and GraphPad PRISM. In patients with CMV reactivation (any detectable and >400IU/ml), the Mann-Whitney test was used to compare time to CMV reactivation between the 2 cohorts. Univariate and multivariate analyses were performed using a competing risk framework as per the methods of Fine and Gray [24]. Death from relapse and non-relapse mortality were treated as competing risks. Tolerability of HD-VALA was assessed via retrospective review of reasons for early cessation.

Results

Sixty-two patients were identified from July 2017 – January 2020; 27 received SD-VALA and 35 received HD-VALA. Patient demographics and transplant characteristics are described in Table 1. A further 10 CMV seronegative patients received transplants from CMV seropositive donors (D+/R-), and per institutional policy were treated with HD-VALA. These patients were not included in the

main analysis but used as comparators in univariable/multivariable analyses, along with 4 D+/R- pairs in the SD-VALA group.

The median duration of CMV follow-up was 216 days from D0 of alloHSCT (range 64-391) in the HD-VALA cohort and 259 days (range 18-708) in the SD-VALA cohort. No patients were lost to follow-up.

Five patients continued HD-VALA after D100, until off immunosuppression. Of these, 1 developed cs-CMVi, and 3 had low-level detectable CMV, but did not reach cs-CMVi. One patient received HD-VALA for 288 days whilst on prolonged corticosteroid to manage synovitis (presumed GVHD).

The cumulative incidence of CMV viremia (any detectable level) was 96% at 100 days post alloHSCT in the SD-VALA group versus 82% in the HD-VALA group (p=0.005) (Figure 1). The cumulative incidence of cs-CMVi at 100 days was 85% in the SD-VALA group versus 37% in the HD-VALA group (p<0.0001) (Figure 2). Of those developing cs-CMVi in the HD-VALA group, 5 (26%) patients had active GVHD, with 3 patients on HD-VALA at onset of cs-CMVi. All 5 were on systemic corticosteroids pre-dating cs-CMVi.

The median time to CMV reactivation (any detectable and cs-CMVi) was significantly longer in the HD-VALA cohort (HD-VALA vs SD-VALA: cs-CMVi median 68 days (range 26-170), n=19 vs 39 days (range 13-68), n=23, p<0.0001; any detectable CMV: median 23 days, n=29 vs 12 days, n=26, p=0.025). Amongst patients who developed CMV viremia, 3 patients (12%) in the SD-VALA and 10 patients (34%) in the HD-VALA cohort did not reach cs-CMVi.

In those requiring pre-emptive CMV therapy, median time from detectable CMV viremia to cs-CMVi was significantly longer in the HD-VALA cohort (35 days (range 8-157 days), n=19 vs 21 days (range 4-40 days), n=23 in SD-VALA cohort, p = 0.04).

In HD-VALA patients developing cs-CMVi, 9 (47%) occurred post-cessation of HD-VALA (median time to occurrence of 76 days (range 62-127) from D0) and 10 (53%) occurred whilst on HD-VALA (median time to occurrence of 49 days (range 26-170 days) from D0). The median duration of HD-VALA administration was 49 days (range 5-67) and 47 days (range 13-156) in the respective cohorts.

One UCB recipient developed gastrointestinal CMV disease in the HD-VALA cohort; this patient initially received effective pre-emptive CMV treatment for elevated viral load >400 IU/ml, occurring whilst on HD-VALA. The CMV disease occurred later when the patient was off CMV prophylaxis. No SD-VALA patients developed CMV disease.

The median duration of HD-VALA administration was 49 days (range 5-288). Nine (26%) patients continued HD-VALA to day +100 and beyond. Intolerance led to early cessation in 17 (49%) (acute

kidney injury, n=8; cytopenia, n=5; gastrointestinal symptoms including nausea, vomiting, diarrhoea, n=3; and both gastrointestinal symptoms and cytopenia, n=1). Other patients ceased due to requirement for definitive CMV therapy (n=8) and unclear reasons (n=1). No patients on SD-VALA ceased due to intolerance. The duration of HD-VALA administration was not significantly associated with CMV reactivation at any detectable level (CMV reactivation yes vs no: median 49 days, n=29 vs 55.5 days, n=6, p=0.91) nor at >400IU/mL (CMV reactivation yes vs no: median 49 days, n=19 vs 84.5 days, n=16, p=0.36).

Univariate analysis found HD-VALA was associated with decreased risk of cs-CMVi (p=0.001), as was D+R- CMV serostatus (p=0.02), while D-R+ CMV serostatus was associated with an increased risk (p=0.04) (Table 2). On multivariate analysis, HD-VALA remained significant for lower risk of cs-CMVi (HR 0.32, p=0.0005) as did D+R- CMV serostatus (HR 0.14, p=0.01) (Table 2).

To account for the differing timing at which HD-VALA was commenced in individual patients, we performed a Cox-regression analysis of time until cs-CMVi, coding HD-VALA usage as a time-dependent variable. This demonstrated that HD-VALA usage was still significantly associated with reduction in cs-CMVi [HR 0.31; 95% CI 0.16-0.60; p=0.0005] within the population.

Fifteen of the 35 patients (43%) had started treatment by day +7 post-alloHSCT (+/-2 days) as planned. Median time to HD-VALA commencement post-transplant was day +14 (range 6-69 days). Reasons for later commencement were renal impairment (n=3), ICU admission (n=2), nausea (n=1), physician concern for renal toxicity potential (n=1), with the majority (n=13) not well-documented.

Discussion

In this study, prophylactic HD-VALA reduced the cumulative incidence of, and prolonged time to cs-CMVi in alloHSCT patients at high-risk of CMV reactivation compared to a historical SD-VALA cohort, despite higher numbers of haploidentical alloHSCT in the HD-VALA cohort. This is relevant as CMV infection is associated with increased non-relapse mortality,[1-9] and although newer prophylaxis strategies have been investigated[15,25-29], there remains a need for accessible, effective alternatives. Reduced requirement for pre-emptive antiviral therapies including val/ganciclovir and foscarnet in the early post-engraftment period may avoid added toxicities and halt cs-CMVi until scheduled weaning of immunosuppression.

In the phase III letermovir prophylaxis trial, a lower rate of cs-CMVi than placebo (19.1% versus 44.3%) was demonstrated, with no differences in toxicity[15]. Letermovir has been adopted as standard prophylaxis in many transplant centres but remains unsubsidised in Australia. Prophylaxis

with Maribavir and brincidofovir showed promise but failed to clearly reduce cs-CMVi in phase III studies[26-29].

CMV reactivation is near universal in umbilical cord blood (UCB) alloHSCT[16]. Hill *et al* retrospectively compared various CMV prophylaxis strategies in seropositive UCB recipients: pre-transplant ganciclovir (5mg/kg daily from day-8 to day-2) followed by aciclovir 500mg/m^2 TDS or 2g valaciclovir TDS until day +100 versus 2g TDS valaciclovir from day 0 to day +100. Cumulative incidence of CMV reactivation was similar between groups, but statistically improved compared to "standard" therapy (500mg BD valaciclovir)[22].

T-cell replete haploidentical alloHSCT represent another high-risk setting, with CMV reactivation occurring in 50-80%[17,18,23]. Hammerstrom *et al* retrospectively compared CMV prophylaxis strategies in haploidentical alloHSCT recipients[23]. Cumulative incidence of CMV reactivation was reduced in the "intensified" group (received 1g TDS of valaciclovir to day+100) compared to the "traditional" group, receiving 500mg valaciclovir daily (67% versus 81%), with a longer median time to CMV reactivation (41 versus 31 days)[23].

High dose valaciclovir prophylaxis has been examined in 2 prospective trials. Ljungman *et al* randomised 727 patients with CMV recipient/donor seropositivity to oral aciclovir 800mg QID or valaciclovir 2g QID until 18 weeks post-alloHSCT. Valaciclovir recipients had reduced CMV infection rates (28% vs 40%), less pre-emptive CMV treatment (23% vs 37%) and delayed time to CMV viremia (HR 0.56)[20,21]. Winston *et al* randomised 168 CMV seropositive alloHSCT recipients to prophylaxis with either 2g QID valaciclovir or IV ganciclovir until day 100 post-alloHSCT. CMV infection rates were not significantly different (12% for valaciclovir versus 19% for ganciclovir) and neutropenia less frequent with valaciclovir (13% vs 32%) suggesting that HD-VALA may be an effective, more tolerable CMV prophylaxis regimen[21].

A recent retrospective analysis compared cs-CMVi in alloHSCT recipients receiving 2g QID valaciclovir prophylaxis versus patients receiving pre-emptive treatment[25]. Some high-risk patients (haploidentical/UCB alloHSCT) were excluded, and lower-risk patients (CMV seronegative recipients) were included. Cumulative incidence of cs-CMVi at 6 months was 20% in those receiving valaciclovir prophylaxis compared with 39% (p=0.009)[25].

Strengths of our analysis include provision of 'real-world' data supporting HD-VALA prophylaxis in CMV-seropositive alloHSCT recipients at high risk of cs-CMVi, where letermovir prophylaxis is not readily accessible. There was often-delayed commencement and limited continuation of HD-VALA to day +100, commonly related to renal impairment, cytopenia or gastrointestinal symptoms. Toxicities

are difficult to attribute to HD-VALA in a retrospective analysis, where concomitant medications may have overlapping toxicity profiles. Prospective analyses have identified HD-VALA toxicities at tolerable levels (renal dysfunction 3-10%, nausea/vomiting/diarrhoea 6-8% and neutropenia 13%)[20,21]. Despite suspected poor tolerability, exposure to HD-VALA appeared protective, evidenced by a reduction and delay in cs-CMVi; and the lack of correlation between HD-VALA duration and rates of cs-CMVi.

Study limitations include lack of information on T-cell reconstitution, concomitant infections, GVHD and immunosuppression (beyond standard post-transplant GVHD prophylaxis) which may have impacted CMV outcomes. Another unaccounted-for consideration is the pill burden of HD-VALA (12 x 500mg tablets daily). Compliance was not assessed systematically, nor the impact of pill burden on a complex post-alloHSCT medical regimen, which should be considered if implementing this approach. Of note, Hawks *et al* recently demonstrated a reduction in cs-CMVi using 1g TDS valaciclovir in alloHSCT recipients, a regimen that could reduce this burden.[30]

Conclusion

In patients at high risk of cs-CMVi undergoing alloHSCT, HD-VALA provides a clinically meaningful improvement in CMV outcomes. We demonstrated a reduced cumulative incidence of cs-CMVi and delayed time to cs-CMVi in patients on HD-VALA. There was also a reduction in use of pre-emptive CMV treatment in the early post-engraftment period when avoidance of additional toxicities is beneficial

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Table 1: Patient Demographics and Transplant Characteristics

	High dose valaciclovir (n=35)	**Standard dose valaciclovir (n=27)**
Median age, years (range)	52 (26-68)	53 (33-68)
Male/Female (%)	24(69) /11 (31)	14(52) /13(48)
Underlying disease (%)		
AML	18 (51)	11 (41)
Myelodysplasia	3 (9)	2 (7)
Myelofibrosis	2 (6)	3 (11)
ALL	1 (3)	4 (15)
Hodgkin Lymphoma	3 (9)	0
Mantle Cell Lymphoma	2 (6)	1 (4)
Other†	6 (17)	6 (22)
CMV serostatus (%)		
D+R+	22 (63)	17 (63)
D-R+	13 (37)	10 (37)
Donor Type (%)		
Matched unrelated	20 (57)	23 (85)
Haploidentical	11 (31)	3 (11)
Sibling	3 (9)	1 (4)
Umbilical cord blood	1 (3)	0
Conditioning Regimen (%)		
Myeloablative	13 (37)	10 (37)

Reduced Intensity / Nonmyeloablative	22 (63)	17 (63)
T-cell depletion (Thymoglobulin)	22 (63)	22 (81)
GVHD prophylaxis		
CNI/MTX	24 (69)	24 (89)
PTCy/CNI/MMF	11 (31)	3 (11)
Mini-Ruutu (Prednisolone)	2 (6)	0

CNI = calcineurin inhibitor, MTX = methotrexate, PTCy = post-transplant cyclophosphamide, MMF= mycophenolate mofetil

† Other diagnoses: aplastic anaemia (2), follicular lymphoma (2), undifferentiated/mixed phenotype acute leukaemia (1), chronic lymphocytic leukemia(1), mixed phenotype acute leukaemia (1), NK/T cell lymphoma(1), chronic myelomonocytic leukaemia (1), T-prolymphocytic leukemia (1), multiple myeloma (1)

Table 2: Univariate / Multivariate Analysis: Factors predicting cs-CMVi

Univariate analysis			
Variable	**HR**	**95% CI**	**P value**
Age (as continuous variable)	1.01	0.99-1.03	0.41
Use of HD VALA	0.35	0.19-0.65	**0.001****
T-cell depletion	1.55	0.79-3.03	0.2
Donor type			
Matched unrelated	1	-	-
Sibling	1.34	0.60-2.96	0.48
Haploidentical	0.78	0.37-1.68	0.54
CMV Serostatus			
D+R+	1	-	-
D-R+	1.47	0.8-2.57	**0.04***
D+R-	0.17	0.04-0.70	**0.02***
Conditioning intensity			
Myeloablative	1	-	-
Reduced intensity/Nonmyeloablative	1.25	0.69-2.27	0.46
Multivariate analysis			
Use of HD VALA	0.32	0.16-0.60	**0.0005*****

CMV serostatus			
D+R+	1	-	-
D-R+	1.38	0.70-2.69	0.35
D+R-	0.14	0.031-0.65	**0.01***

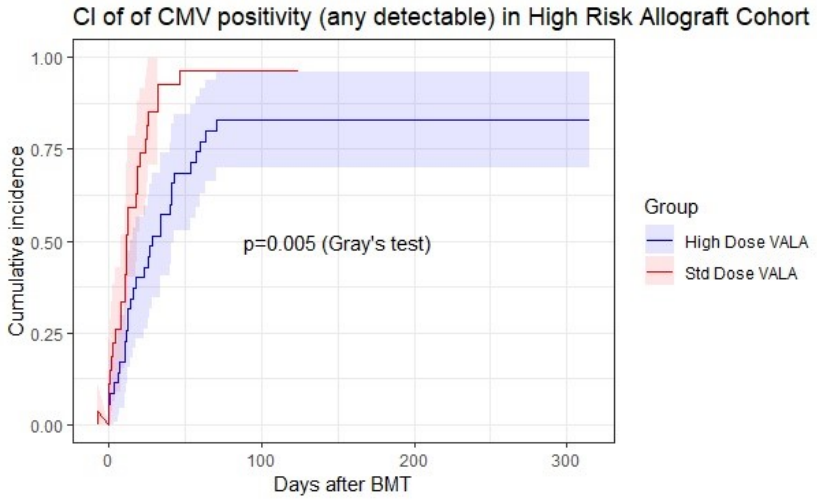

Figure 1: Cumulative incidence of any detectable CMV reactivation was significantly lower in the HD-VALA cohort compared to the SD-VALA cohort

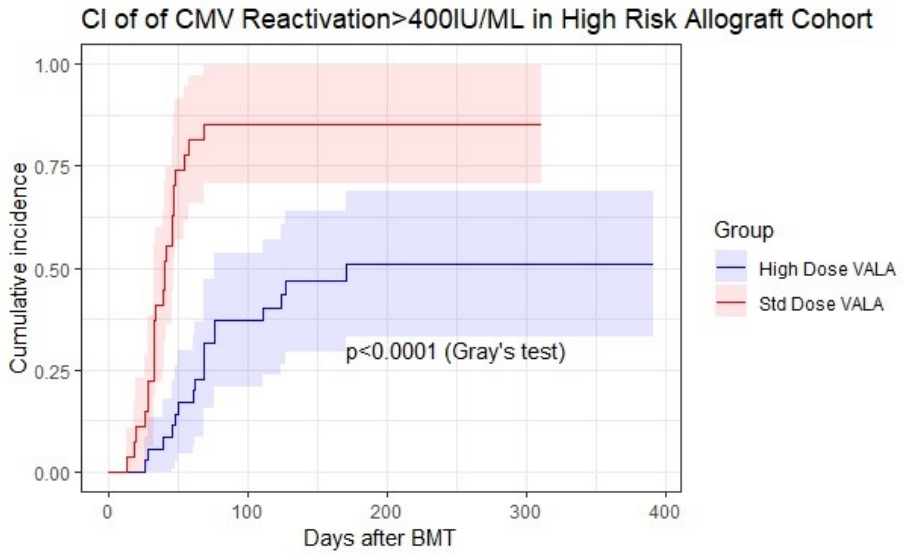

Figure 2: Cumulative incidence of cs-CMVi (CMV viral load >400IU/ml) was significantly lower in the HDVALA in comparison to the SD-VALA cohort