Control of cytomegalovirus viremia after T cell depleted allogeneic stem cell transplantation

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Chapter 2

Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients

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Abstract

The efficacy and safety of oral valganciclovir was compared to ganciclovir i.v. in pre-emptive treatment of cytomegalovirus (CMV) in T cell depleted allogeneic stem cell transplant (alloSCT) recipients. A therapeutic guideline was developed to allow the safe application of valganciclovir in alloSCT recipients requiring CMV therapy. In total, 107 consecutive transplant recipients were evaluated. Cytomegalovirus DNA load in plasma was monitored longitudinally; details on antiviral therapy and treatment responses were analyzed retrospectively. Fifty-seven CMV treatment episodes were recorded in 34 patients: 20 with valganciclovir (900 mg twice-daily) and 37 with ganciclovir (5 mg/kg twice-daily). Median CMV DNA load reduction was 0.079 and 0.069 $\log_{10}$copies/ml/ day in the ganciclovir and valganciclovir group, respectively. Good response on CMV DNA load (reduction below 3.0 $\log_{10}$ copies/ml) was observed in 75.7% of ganciclovir and 80.0% of valganciclovir treatment episodes. Severe adverse effects were not observed and CMV-related disease did not occur. However, the percentage of patients receiving erythrocyte transfusion was higher in the group of patients receiving ganciclovir as compared to valganciclovir (41 versus 20%, P=0.116). In conclusion, pre-emptive treatment with valganciclovir and ganciclovir, led to similar reduction of CMV DNA load. Oral valganciclovir is an attractive and safe alternative for pre-emptive CMV treatment in T cell depleted allo- SCT recipients.

Introduction

In myeloablative (MA) allogeneic stem cell transplant (alloSCT) recipients, cytomegalovirus (CMV) infection contributes significantly to morbidity and mortality.[1] Primary infection results in a lifelong persistence of the virus with reactivation and potentially fatal disease when immunity fails. Cytomegalovirus seropositivity in a patient before transplantation is associated with the highest risk of CMV disease.[2] Furthermore, graft-versus-host disease (GVHD) and T cell depletion (TCD) of the transplant are important contributing factors.[3] Current strategies for the prevention of CMV disease aim at preventing end-organ disease by using ganciclovir or valganciclovir prophylaxis[4,5] or ganciclovir pre-emptive therapy, initiated upon early detection of CMV infection by antigenemia or CMV DNA in plasma.[5,6] The relative merits of both strategies have been debated extensively in the literature.[7,8] The major drawback limiting the use of oral ganciclovir is its poor bioavailability, which precludes therapeutic use by oral administration.[6] This has now changed with the introduction of valganciclovir, which is an orally administered prodrug of ganciclovir with good bioavailability. Previous pharmacokinetic studies showed similar drug exposure to ganciclovir after a single oral dose of 900 mg valganciclovir as compared to an intravenous dose of 5mg/kg ganciclovir.[9–11] Recently, oral valganciclovir and intravenous ganciclovir were shown to have similar efficacy in pre-emptive CMV treatment in solid organ transplant recipients.[12–14] As a consequence, the prevention of CMV disease in high-risk renal, renal–pancreas and heart transplant patients was added as another indication to the original approval of valganciclovir for the treatment of CMV retinitis in AIDS patients. So far, no data are available on the efficacy of 900 mg valganciclovir twice daily as compared to intravenous 5 mg/kg ganciclovir twice daily in the pre-emptive therapy of CMV infection in stem cell transplant recipients and therefore valganciclovir is not licensed for use in alloSCT patients. A comparison with intravenous ganciclovir in alloSCT patients is warranted, as hematological toxicity is a common side effect of ganciclovir and of particular significance in this population. In this observational prospective study, we compared the efficacy and safety of CMV DNA load-guided pre-emptive therapy with valganciclovir to ganciclovir intravenously in alloSCT recipients.

Patients and methods

Patients

All consecutive patients undergoing MA and reduced-intensity allogeneic stem cell transplantation at the Leiden University Medical Center between January 2001 and December 2004 were included in this analysis. All patients at risk for CMV infection (i.e. CMV seropositivity in either the recipient (R^+), the donor (D^+) or both (D^+R^+)) were routinely monitored by CMV DNA load detection in plasma. Data were available on demographic characteristics, underlying diseases, donor and recipient CMV serostatus, occurrence

of GVHD and treatment (i.e. initiation, duration, type and dosage of drugs used) and the ganciclovir formulation (i.e. valganciclovir or ganciclovir), CMV DNA load measurements and general laboratory parameters.

Transplantation

T cell depleted transplantation was performed either according to a reduced-intensity conditioning (RIC) protocol or a conventional MA regimen as described previously.[15,16] The RIC regimen consisted of fludarabine (30 mg/m^2 , intravenously, days -10 to -6), busulphan (3.2 mg/kg, intravenously, days -6 and -5) and ATG (10 mg/kg/day intravenously, days -4 to -1), for both sibling and matched unrelated donor (MUD) grafts. The MA conditioning regimen consisted of cyclophosphamide (60 mg/kg/day intravenously for 2 consecutive days) followed by single dose of total body irradiation (TBI, 9 Gy, day -1) in patients receiving sibling donor grafts. Recipients of MUD grafts, in the MA regimen, received additional Campath- 1G or -1H (days -8 and -4) and cyclosporine (3mg/kg intravenously, starting on day -1) and TBI (6 Gy, days -8 and -7). The stem cell product was infused on day 0. In all conditioning regimens, TCD of the graft was performed by in vitro incubation of the graft with Campath-1H (20 mg). Assessment of acute and chronic GVHD was performed using the Glucksberg and Shulman criteria.[17,18] In the absence of GVHD or graft failure, patients received donor lymphocyte infusion (DLI) after RIC transplantation or in mixed chimerism or relapsed disease after MA transplantation. Donor lymphocyte infusion was administered at least 6 months following transplantation. Donor lymphocyte infusion was not used as a therapeutic modality for CMV infection.

Cytomegalovirus monitoring and treatment

CMV DNA load was measured at weekly intervals for at least 180 days following transplantation, until death occurred or beyond day 180 until CMV DNA became undetectable. The real-time quantitative PCR for detection of CMV DNA in plasma was performed according to the method described previously.[19] Cytomegalovirus DNA load-guided pre-emptive therapy was initiated according to a guideline as described previously.[13] In short, any symptomatic CMV infection would be treated with intravenous 5 mg/kg ganciclovir twice daily. In case of a first reactivation or a significant viraemia (CMV DNA load >10^4 copies/ml, or CMV load >10^3 copies/ml and more than 1.0 $\log_{10}$ increase as compared to preceding measurement) without clinical symptoms of CMV disease, either 900 mg valganciclovir twice daily or intravenous 5 mg/kg ganciclovir twice daily was administered for 2 weeks. Until 2003 intravenous ganciclovir was used as primary pre-emptive treatment. From 2003 onwards, as soon as it became available for clinical use, valganciclovir was used as preferred primary treatment of outpatients, only limited to approval by the patients' medical insurance. When such approval was not granted, or if hospital admission was indicated for other reasons, intravenous ganciclovir was administered. Ganciclovir and valganciclovir dosages were adjusted to renal function as described previously.[20] During (val)ganciclovir treatment, CMV

DNA load and hematological parameters were monitored at least weekly; G-CSF prophylaxis was not routinely used. Donor lymphocyte infusion was not used as a therapeutic modality for CMV infection.

End points and statistical analysis

The effect of CMV treatment on CMV DNA load in plasma, following a full course of either ganciclovir or valganciclovir, was defined as good response (CMV DNA load reduction of more than 0.5 $\log_{10}$ and to a level below 3.0 $\log_{10}$ copies/ml), moderate response (reduction of CMV DNA load of more than 0.5 $\log_{10}$, but not to a level below 3.0 $\log_{10}$ copies/ml) and no response (equal DNA load (i.e. reduction of less than 0.5 $\log_{10}$) or an increase). The levels of 3.0 $\log_{10}$ and 0.5 $\log_{10}$ were chosen as reference values based on a previous report on pre-emptive CMV treatment in SCT recipients.[19] In addition, absolute reduction in number of CMV DNA copies/ml was calculated to compensate for differences in baseline CMV load before treatment. To avoid bias owing to possible differences in CMV reduction rate in first episodes as compared to subsequent episodes, the effect of antiviral medication in first and subsequent episodes was analyzed separately. Cytomegalovirus load reduction per day was calculated by dividing the difference in pre- and post-treatment CMV DNA load by the number of treatment days.

Hematological toxicity was assessed by comparing the number of erythrocyte and thrombocyte transfusion units administered during and following antiviral treatment and by comparing leucocyte ratios (calculated by dividing the leucocyte count before treatment by the count at the end of treatment). Criteria for erythrocyte and thrombocyte transfusion were hemoglobin concentration below 6.0 mmol/l and platelet count below 10 x 10^{10}/l, respectively. Definitions of CMV infection, CMV disease and CMV detection in blood were consistent with internationally accepted criteria.[21]

All statistical analyses were performed using SPSS version 12.0.1. Differences in the distribution of categorical data were tested using χ^2 test. For comparison of the antiviral effect between the two treatments (i.e. ganciclovir or valganciclovir) and comparison of baseline non-categorical data we used Mann–Whitney U-test. Paired observations (e.g., pre-treatment versus post treatment measurements) were analyzed non-parametrically using the Wilcoxon signed ranks test for paired observations.

Results

A total of 107 patients were included in this study. The demographic and disease characteristics for both CMV treatment groups are shown in **Table 1**. Distribution of the characteristics across the two groups was similar. Briefly, 48 patients received a transplantation following an RIC protocol, whereas 59 patients received their transplants following an MA conditioning regimen. With regard to donor and recipient CMV serostatus, 40 D^+R^+ (37.4%), eight D^+R^- (7.5%), 30 D^-R^+ (28.0%) and 29 D^-R^- (27.1%) combinations were observed. The D^-R^- patients were excluded from further analysis, as they are not considered

to be at risk for CMV infection. The median follow-up period following transplantation was 200 days (range: 30–611). During the follow-up period, CMV DNA load became detectable in 42 out of 78 (54%) patients at risk for CMV infection, resulting in 57 CMV treatment episodes with either ganciclovir or valganciclovir in 34 patients. The incidence of GVHD and the percentage of patients treated for GVHD were similar in the two CMV treatment groups. In none of the patients DLI was administered during treatment episodes.

The CMV treatment results are shown in **Table 2**. Intravenous ganciclovir was used in 37 episodes. A good response was observed in 28 episodes (76%). A moderate response was observed in five episodes (14%) occurring in four separate patients. One of these patients died as a result of extensive GVHD without signs of CMV disease. The remaining three patients reached a good response following a second course of intravenous ganciclovir. In four ganciclovir treatment episodes (11%), occurring in four individual patients, no response on CMV load was observed. In three of these four non-responding patients, CMV DNA load decreased below undetectable levels within 2 weeks after cessation of ganciclovir. In the remaining patient, CMV DNA load increased from 3.5 to 4.8 $\log_{10}$ copies/ml, despite 4 weeks of ganciclovir treatment, and subsequently foscarnet was administered, resulting in a CMV DNA load below detectable levels within 14 days of treatment. Treatment with valganciclovir was administered in 20 of the 57 episodes, resulting in a good response in 16 out of these 20 episodes (80%). Moderate response was observed in three out of these 20 episodes (15%) occurring in three individual patients. One of these patients died as a result of extensive GVHD without signs of CMV disease, and the remaining two patients showed a good response following a second course of valganciclovir. In one out of the 20 valganciclovir treatment episodes (5%), no response on CMV DNA load was observed; this patient showed a good response upon a second course of valganciclovir.

Table 1. Characteristics of the study population in both treatment groups. In total, 57 CMV treatment episodes were observed in 34 patients. No statistically significant differences were observed between the two treatment groups. Systemic treatment of GVHD consisted of oral prednisone, intravenous methylprednisolone and/or oral cyclosporine. (CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; MM: multiple myeloma; NHL: non-Hodgkin lymphoma).

Parameter		ValGCV	GCV
Treatment episodes, n		20	37
Number of patients, n		14	26
Median age in years (range)		51 (41-62)	50 (24-62)
Male gender, n (%)		9 (64)	17 (65)
Type of conditioning, n (%)	Reduced intensity	6 (40)	14 (54)
	Myeloablative	8 (60)	12 (46)
Type of donor, n (%)	Related	11 (80)	20 (76)
	Unrelated	3 (20)	6 (24)
Underlying disease, n (%)	Acute leukemia	5 (38)	9 (35)
	CML	2 (14)	3 (12)
	CLL	1 (7)	1 (4)
	MM	1 (7)	6 (23)
	NHL	4 (29)	1 (4)
	Other	1 (7)	6 (23)
GvHD, n (%)	No GVHD	10 (70)	19 (73)
	Grade I/II	4 (25)	6 (24)
	Grade III/IV	1 (5)	1 (3)
	Treatment	3 (20)	5 (19)
CMV serostatus, n (%)	D^+R^-	0 (0)	1 (3)
	D^+R^+	7 (50)	13 (51)
	D^-R^+	7 (50)	12 (46)
Median duration of treatment in days (range)		14 (7-36)	14 (7-28)
Hematological parameters at start of treatment [Median values (range)]	Hemoglobin (mmol/L)	7.3 (5.1-8.3)	6.9 (4.5-10.6)
	Leucocyte count (x109/L)	5.0 (1.9-8.0)	3.1 (0.7-11.5)
	Thrombocyte count (x109/ L)	88.0 (62.0-264.0)	100 (12.0-206.0)

Table 2. Characteristics of 57 CMV treatment episodes in 34 patients and response on CMV DNA load according to treatment group (valGCV: valganciclovir; GCV: ganciclovir). No statistically significant differences were observed between the two treatment groups.

Parameter		valGCV (n = 20)	GCV (n = 37)
First treatment episodes, n (%)		8 (40)	26 (70)
Subsequent treatment episodes, n (%)		12 (60)	11 (30)
Response on CMV DNA load	Good response, n (%)	16 (80)	28 (76)
	Moderate response, n (%)	3 (15)	5 (14)
	No response, n (%)	1 (5)	4 (11)
Erythrocyte transfusion, n (%)		4 (20)	15 (41)
Thrombocyte transfusion, n (%)		3 (15)	5 (14)
Leucocyte ratio* (median, range between parenthesis)		1.6 (0.6-27.1)	1.2 (0.2-11.0)
Leucocyte count x109/l (median, range between parenthesis)	Pre-treatment	5.0 (1.9-8.0)	3.1 (0.7-11.5)
	Post-treatment	3.6 (0.1-9.7)	3.0 (0.4-8.6)

*Calculated by dividing leucocyte count before treatment by the count and the end of treatment.

The effect of anti-CMV treatment with ganciclovir and valganciclovir was further assessed by comparing the CMV DNA load at the start and at the completion of the treatment episode. When first treatment episodes as well as all subsequent episodes were evaluated, CMV DNA load at start of therapy in the ganciclovir and the valganciclovir group was similar (median 4.3 (range: 3.3–6.2) and 4.2 $\log_{10}$ copies/ml (range: 3.1–5.7), P>0.4, respectively, Figure 1b). The kinetics of CMV DNA following treatment with ganciclovir and valganciclovir for individual patients are shown in **Figure 1a**. A median reduction of 1.20 and 1.10 $\log_{10}$ DNA copies/ml was reached in the ganciclovir- (n = 37) and the valganciclovir- (n = 20) treated patients, respectively (P<0.0001 for both groups). No difference in the magnitude of CMV DNA load reduction/treatment day was observed between the ganciclovir and valganciclovir groups (median 0.0786 (range: -0.0464–0.767) and 0.0690 $\log_{10}$ copies/ml/day (range: 0.0182–0.171), P>0.8, respectively; **Figure 1b**). Cytomegalovirus treatment episodes were further subdivided into 34 first episodes (26 ganciclovir, eight valganciclovir) and 23 subsequent episodes (11 ganciclovir, 12 valganciclovir) (**Figure 2a**). Cytomegalovirus DNA load at start of therapy, according to treatment episode, was similar in the ganciclovir and valganciclovir groups (median 4.4 (range: 3.3–5.6) versus 4.1 $\log_{10}$ copies/ml (range: 3.1–5.1) in first episodes, P>0.3, respectively and 4.3 (range: 3.5–5.7) versus 4.3 $\log_{10}$ copies/ ml (range: 3.5–5.7) in subsequent episodes, P>0.7, respectively). The magnitude of CMV load reduction/ treatment day in first treatment episodes was similar for the ganciclovir and valganciclovir group (median 0.0941 (range: 0.000–0.767) and 0.0833 $\log_{10}$ copies/ml/day (range: 0.0381–0.171), P>0.6, respectively, Figure 2b). For subsequent episodes, the same

result was obtained (median 0.0786 (range: -0.0464–0.260) and 0.0685 log_{10} copies/ml/ day (range: 0.0182–0.150), P>0.4, for ganciclovir and valganciclovir, respectively; **Figure 2b**).
Erythrocyte transfusions were administered in 15 out of the 37 (41%) ganciclovir treatment episodes (median number of units: 2, range 2–6 units) as compared to four out of the 20 (20%) (median number of units: 2, range 2–6 units) of the valganciclovir treatment episodes (P = 0.116). The percentage of patients receiving thrombocyte transfusions was similar in the ganciclovir- and valganciclovir- treated groups (15.0 and 13.5%, P40.8, respectively). Furthermore, the leucocyte ratio was not significantly different between ganciclovir and valganciclovir treatment episodes (median 1.16 and 1.55, P > 0.1, respectively).
No signs of CMV disease and no severe adverse reaction (NCI grade 3–4) of (val)ganciclovir treatment were observed.

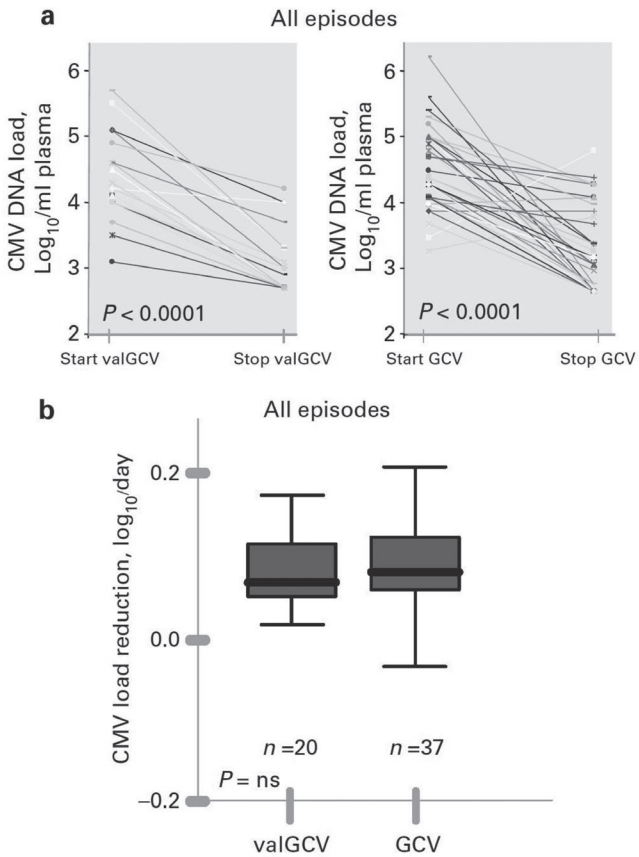

Figure 1.
In panel A, the course of CMV DNA load before and after treatment with valganciclovir or ganciclovir for individual patients is shown (all treatment episodes).
In panel B, the CMV DNA load reduction per treatment day with valganciclovir (ValGCV) and intravenous ganciclovir (GCV) is shown (all treatment episodes). The box plots display the median, the 25th and 75th percentiles (box), and the smallest and largest values (whiskers).

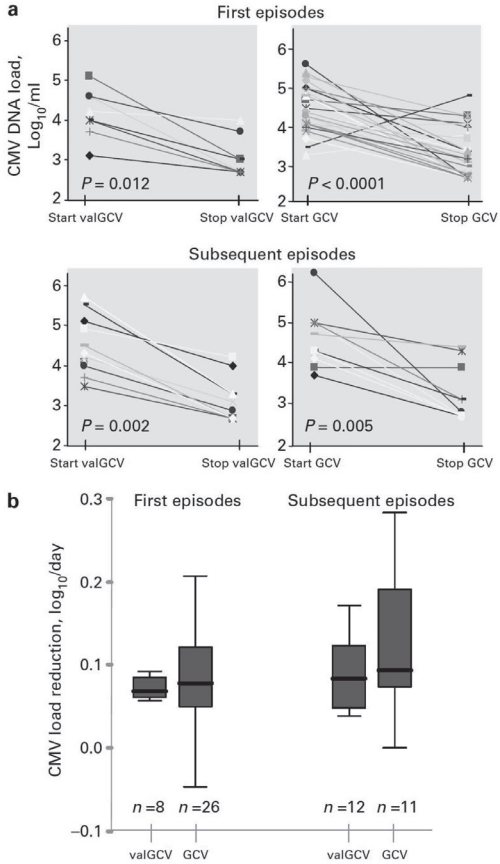

Figure 2.
In panel A, the courses of CMV DNA load before and after treatment with valganciclovir or ganciclovir for individual patients are shown. First (upper panel) and subsequent (lower panel) treatment episodes are plotted separately. In panel B, the CMV DNA load reduction per day during treatment with valganciclovir (ValGCV) and intravenous ganciclovir (GCV). First (left box plots) and subsequent (right box plots) episodes are shown separately. The box plots display the median, the 25th and 75th percentiles (box), and the smallest and largest values (whiskers). No significant differences are present.

Discussion

This study demonstrates that pre-emptive treatments with oral valganciclovir and intravenous ganciclovir are equally effective in reducing CMV DNA load in allogeneic stem cell recipients. Pre-emptive treatment of CMV viraemia episodes in allogeneic stem cell recipients with either valganciclovir or ganciclovir led to a similar median CMV DNA load reduction in plasma of approximately 0.1 $\log_{10}$ copies/ml/day, which is in accordance with our previous report on renal and renal/pancreas transplant recipients.[13]

Although initially no response was seen upon treatment with intravenous ganciclovir in four patients, CMV DNA load spontaneously declined in three of these whereas in only one patient a switch to foscarnet was made. Furthermore, in four other patients (five treatment

episodes), treatment with intravenous ganciclovir for 14 days did not reduce the CMV DNA load below the level of 3.0 $\log_{10}$ copies/ml and a subsequent course was needed to further reduce CMV DNA load. Similarly, in four patients treated with valganciclovir, either a subsequent course or a switch to foscarnet was needed to reduce CMV DNA load beyond detectable levels. Reasons for these failures are not clear and this study was not designed to identify factors associated with antiviral treatment failure. Therefore, further investigation with regard to these treatment failures is warranted.

As soon as valganciclovir became available in our institution in 2003, it was used as preferred primary treatment of asymptomatic patients, only limited to approval by the patient's medical insurance. In case such an approval was not granted or in case of co-morbidity leading to hospitalization, intravenous ganciclovir was administered. Patient selection might therefore have occurred, as co-morbidity was more likely to be present in admitted patients treated with ganciclovir. However, we do not expect that this possible bias has influenced our results to such an extent that the conclusions drawn might be incorrect. The baseline CMV loads in the ganciclovir- and valganciclovir-treated groups were similar, indicating similar CMV activity. Furthermore, the magnitude of CMV decline in all analyzed subgroups was similar, substantiating our conclusion on the equal efficacy of both drugs in CMV infection.

In our study, the hematological toxicity of oral valganciclovir in alloSCT patients was similar as compared to ganciclovir intravenously. The slightly higher, although not statistically significant, percentage of patients receiving erythrocyte transfusions in the intravenous ganciclovir group might be the result of co-morbidity in the admitted patients treated with ganciclovir intravenously. Mainly owing to the retrospective nature of this study, differences in non-hematological toxicity, such as gastrointestinal and neurological complications, between the two treatment groups could not be assessed adequately and further evaluation in a prospective study is warranted.

So far, no other studies have been reported on the use of valganciclovir compared to intravenous ganciclovir in stem cell recipients. In conclusion, based on our findings, oral valganciclovir (900 mg, twice daily) is equally effective and safe as intravenous ganciclovir (5 mg/kg, twice daily) in the pre-emptive treatment of CMV disease following alloSCT. There is an urgent need for an effective oral treatment for pre-emptive CMV therapy, which would enable prevention and treatment of CMV in an outpatient setting leading to reduced patient burden and health-care cost. The finding of the therapeutic equivalence of oral valganciclovir and intravenous ganciclovir is a confirmation of previous reports with respect to pre-emptive[12–14, 22] and prophylactic treatment[20] in solid organ transplant recipients.

The large majority of alloSCT recipients, without any signs and symptoms of CMV disease when the first laboratory signs of CMV infection are detected, can benefit from treatment with an oral drug, without the need of hospitalization. Based on rational precautions, intravenously administered ganciclovir remains the first choice drug for patients with suspected symptomatic CMV infections, as the course of CMV disease can be serious, rapidly progressive and ultimately fatal.

References

1. Razonable RR. Epidemiology of cytomegalovirus disease in solid organ and hematopoietic stem cell transplant recipients. Am J Health Syst Pharm 2005; 62 (8 Suppl 1): S7–S13.
2. Boeckh M, Nichols WG. The impact of cytomegalovirus serostatus of donor and recipient before hematopoietic stem cell transplantation in the era of antiviral prophylaxis and preemptive therapy. Blood 2004; 103: 2003–2008.
3. Gandhi MK, Khanna R. Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. Lancet Infect Dis 2004; 4: 725–738.
4. Goodrich JM, Bowden RA, Fisher L, Keller C, Schoch G, Meyers JD. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med 1993; 118: 173–178.
5. Ljungman P. Beta-herpesvirus challenges in the transplant recipient. J Infect Dis 2002; 186 (Suppl 1): S99–S109.
6. Crumpacker CS. Ganciclovir. N Engl J Med 1996; 335: 721–729.
7. Emery VC. Prophylaxis for CMV should not now replace pre-emptive therapy in solid organ transplantation. Rev Med Virol 2001; 11: 83–86.
8. Hart GD, Paya CV. Prophylaxis for CMV should now replace pre-emptive therapy in solid organ transplantation. Rev Med Virol 2001; 11: 73–81.
9. Brown F, Banken L, Saywell K, Arum I. Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. Clin Pharmacokinet 1999; 37: 167–176.
10. Pescovitz MD, Rabkin J, Merion RM, Paya CV, Pirsch J, Freeman RB et al. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. Anti- microb Agents Chemother 2000; 44: 2811–2815.
11. Jung D, Dorr A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. J Clin Pharmacol 1999; 39: 800–804.
12. Devyatko E, Zuckermann A, Ruzicka M, Bohdjalian A, Wieselthaler G, Rodler S et al. Pre-emptive treatment with oral valganciclovir in management of CMV infection after cardiac transplantation. J Heart Lung Transplant 2004; 23: 1277–1282.
13. Kalpoe JS, Schippers EF, Eling Y, Sijpkens YW, de Fijter JW, Kroes AC. Similar reduction of cytomegalovirus DNA load by oral valganciclovir and intravenous ganciclovir on pre-emptive therapy after renal and renal-pancreas transplantation. Antivir Ther 2005; 10: 119–123.
14. Singh N, Wannstedt C, Keyes L, Gayowski T, Wagener MM, Cacciarelli TV. Efficacy of valganciclovir administered as preemptive therapy for cytomegalovirus disease in liver transplant recipients: impact on viral load and late-onset cytomegalovirus disease. Transplantation 2005; 79: 85–90.
15. Barge RM, Osanto S, Marijt WA, Starrenburg CW, Fibbe WE, Nortier JW et al. Minimal GVHD following in-vitro T cell depleted allogeneic stem cell transplantation with reduced- intensity conditioning allowing subsequent infusions of donor lymphocytes in patients with hematological malignancies and solid tumors. Exp Hematol 2003; 31: 865–872.

16. Barge RM, Brouwer RE, Beersma MF, Starrenburg CW, Zwinderman AH, Hale G et al. Comparison of allogeneic T cell depleted peripheral blood stem cell and bone marrow transplantation: effect of stem cell source on short- and long- term outcome. Bone Marrow Transplant 2001; 27: 1053–1058.
17. Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. Transplantation 1974; 18: 295–304.
18. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 1980; 69: 204–217.
19. Kalpoe JS, Kroes AC, de Jong MD, Schinkel J, de Brouwer CS, Beersma MF et al. Validation of clinical application of cytomegalovirus plasma DNA load measurement and definition of treatment criteria by analysis of correlation to antigen detection. J Clin Microbiol 2004; 42: 1498–1504.
20. Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B et al. Efficacy and safety of valganciclovir vs oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 2004; 4: 611–620.
21. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 2002; 34: 1094–1097.
22. Mattes FM, Hainsworth EG, Geretti AM, Nebbia G, Prentice G, Potter M et al. A randomized, controlled trial comparing ganciclovir to ganciclovir plus foscarnet (each at half dose) for pre-emptive therapy of cytomegalovirus infection in transplant recipients. J Infect Dis 2004; 189: 1355–1361.