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Artículo original

Valganciclovir for the prophylaxis of cytomegalovirus infection early after allogenic stem cell transplantation

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RESUMEN

Estudio prospectivo, efectuado en 30 pacientes seropositivos para citomegalovirus que recibieron valganciclovir a la dosis de 900 mg por día, cinco días a la semana, comenzando en los días 21 a 35 luego del trasplante alogénico y continuando hasta el día 100 postrasplante. Veinticinco de los 30 pacientes (80%) tenían mayor riesgo de infección debido a que recibieron: alemtuzumab (n=9), esteroides para el tratamiento de la enfermedad de injerto contra huésped (n=12) o uso de donador no relacionado (n=12). Los pacientes se monitorizaron con prueba semanal de reacción en cadena de polimerasa (PCR) en un laboratorio central para conocer la concentración de citomegalovirus. Cinco pacientes tuvieron toxicidad a la médula ósea relacionada con el valganciclovir (menos de 1,000 neutrófilos por µL = 1, menos de 50,000 plaquetas por µL = 4). La infección por citomegalovirus ocurrió en cuatro pacientes sin ninguna evidencia de enfermedad invasiva. Los nuevos estudios diagnósticos han mejorado la detección y el diagnóstico de las infecciones por citomegalovirus. A pesar de estos adelantos, aproximadamente 5% de los pacientes que reciben terapia preventiva contra citomegalovirus resultan con enfermedad invasiva a los pulmones, hígado, tubo gastrointestinal u otros órganos. La prescripción más frecuente de fármacos inmunosupresores potentes y el uso de donadores alternos han aumentado la incidencia de infección por citomegalovirus. En conclusión, el valganciclovir en las dosis utilizadas en este estudio es bien tolerado con incidencia baja y reversible de mielosupresión. Además, la incidencia de infección con citomegalovirus fue baja en este grupo de pacientes en riesgo alto de infección por citomegalovirus.
Palabras clave: valganciclovir, profilaxis, citomegalovirus, infección, trasplante alogénico.

ABSTRACT

Despite improvements in methods for the early diagnosis of Cytomegalovirus (CMV) infection, 5% of allogeneic stem cell transplant patients receiving preemptive therapy develop CMV disease. In addition, the use of highly immunosuppressive and the use of mismatched donors have increased the incidence of CMV infection and disease. Thirty CMV seropositive patients participated in a prospective trial evaluating the safety and efficacy of oral valganciclovir administered at 900 mg daily 5 days a week starting 21 to 35 days after transplant and continuing through Day 100 post transplant. Twenty-four of 30 (80%) patients had other risk factors for the development of CMV infection including: use of alemtuzumab (n=9), corticosteroid therapy for treatment of graft versus host disease (n=12), or unrelated donor transplant (n=12). Patients were monitored with weekly quantitative CMV PCR analysis at a central lab. Five patients developed myeloid toxicity related to valganciclovir (absolute neutrophil count < 1,000/µL = 1, platelets < 50,000/µL = 4). CMV infection occurred in 4 patients with no CMV disease in any of the patients. We conclude that valganciclovir at the dose used in this study is well tolerated with minimal, reversible myelosuppression. The incidence of CMV infection with valganciclovir prophylaxis was low in this high-risk group.
Key words: Valganciclovir, prophylaxis, cytomegalovirus infection, allogeneic stem cell transplantation.

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Cytomegalovirus prophylaxis with intravenous ganciclovir was studied previously and was associated with a decreased incidence of CMV infection and disease but at the cost of increased myelosuppression, risk of infection, and in some trials, increased mortality.[1-8] These side effects of ganciclovir, coupled with the need for intravenous administration and improvements in detection techniques has made preemptive therapies the most common method of CMV prevention.[9]

However, preemptive therapy for CMV is associated with systemic CMV disease in up to 5% of patients, frequently

associated with serious morbidity and mortality.[10,11] As newer strategies in stem cell transplantation have increased the degree of immunosupression there has been a concomitant increase in the incidence of CMV infection and disease. The increased use of alternative donors, in vivo and in vitro T-lymphocyte depletion techniques including T-cell purging, and highly immunosuppressive drugs such as alemtuzumab, antithymocyte globulin, and fludarabine all increase the risk of viral reactivation post transplant.[12-14] The use of alternative donors and peripheral blood stem cell transplants have also increased the incidence of chronic graft versus host disease and its associated need for prolonged corticosteroid therapy.

Valganciclovir is a valine esther of ganciclovir that is hydrolyzed to ganciclovir after oral administration. A dose of 900 mg of valganciclovir orally provides a dose equivalent to 5 mg/kg of intravenous ganciclovir.[14-16] Valganciclovir has been shown to be as effective as oral ganciclovir in the treatment and prevention of CMV infection and disease in organ transplant and AIDS patients.[18] There are limited reports on the use of valganciclovir after allogeneic stem cell transplant. Studies by Einsele and colleagues have shown that the bioavailability of valganciclovir after allogeneic stem cell transplant is affected on patients with intestinal GVHD.[19] Patients with intestinal GVHD had lower exposure to ganciclovir after oral valganciclovir when compare to patients receiving intravenous ganciclovir. Despite this difference, the effectiveness in clearance of CMV from the blood was similar in patients receiving valganciclovir or IV ganciclovir in the preemptive treatment of CMV reactivation.

The use of valganciclovir for the prophylaxis of CMV in high-risk patients could decrease the incidence of CMV infection without the need for intravenous drugs. We are now reporting the results of a single arm trial evaluating the safety and efficacy of valganciclovir for the early prophylaxis (<100 days after transplant) of CMV infection and disease after allogeneic stem cell transplant.

MATERIAL AND METHODS

Thirty patients from 3 centers were enrolled in this trial. At these centers, non-eligible patients received preemptive therapy with intravenous ganciclovir or valganciclovir per institutional standards. Eligible patients included CMV seropositive recipients or CMV seronegative recipients of CMV seropositive grafts. Other inclusion criteria included estimated creatinine clearance of ≥50 mL/min, platelet count ≥50,000/μL, and WBC count ≥ 1,000/μL at the start of prophylaxis. Valganciclovir prophylaxis started between days 21 and 35 post transplant and after myeloid recovery from their conditioning regimen. Patients received valganciclovir at 900 mg daily 5 days a week until day 100 post transplant. For patients weighing 30-50 kg, dosing of valganciclovir was reduced to 450 mg orally 5 days/week. CMV monitoring consisted of weekly quantitative plasma CMV PCR performed at a central lab according to the Amplicor® CMV test (Roche Diagnostics). Threshold for positivity was ≥ 1000 copies/mL.

Management of myelosuppression

For neutrophil counts below 1,000/μL or platelets below 50,000/μL, valganciclovir therapy was temporarily discontinued. Causes other than valganciclovir myelosuppresion were investigated including tumor recurrence, effect of concomitant drugs and infections. G-CSF was allowed at the discretion of the principal investigator.

Valganciclovir was restarted at 900 mg 3 days a week if the ANC increased to 1,000/μL or if the platelet count increased to 50,000/μL after stopping valganciclovir and if neutropenia or thrombocytopenia were considered to be due to valganciclovir toxicity. Patients were taken off study if neutropenia lasted more than 7 days. If myelosuppression non-related to valganciclovir resolved, study drug was restarted at dose used prior to development of neutropenia or thrombocytopenia.

Dose modifications for patients developing impaired renal function

*Cr Cl (mL/min)	Dose for patients >50 kg
≥ 50	900 mg M®F
40-49	450 mg M®F
25-39	450 mg MWF
≤ 24	Off study

*Cr Cl = measured creatinine clearance

Statistical Analysis

The primary objective of the study was to determine the incidence of neutropenia associated with the use of val-

ganciclovir. Neutropenia was defined as ANC <1,000/µL. The goal was to have an incidence of neutropenia of less than 30% (unrelated to disease progression, infections or other drugs). That incidence would be an approximately 50% reduction on the incidence of neutropenia associated with the use of IV gancicyclovir in the prophylaxis setting.

A sample size of 30 achieved 91% power to detect a difference of 0.3 between the null hypothesis proportion of 0.6 and the alternative hypothesis proportion of 0.3 using a two-sided, binomial hypothesis test with a target significance level of 0.05 (the actual significance level is 0.03842; beta value = 0.08447).

RESULTS

Patient characteristics

Thirty patients from three institution participated in the study. All patients were enrolled after signing Institutional Review Board approved consent forms. Most common reason for not enrolling patients were not meeting eligibility criteria due to increased creatinine clearance or pancytopenia. Patient characteristics are described in Table 1. All patients were CMV seropositive prior to transplant. Median age for the group was 53 years (range 14-70). Stem cell source included peripheral blood (n=26) or bone marrow (n=4). Donor source included match-related sibling (n=18), or match-unrelated donors (n=12). Patients on the study received ablative (n=17) or reduced intensity conditioning regimens (n=13). Twenty-four of 30 (80%) patients had other risk factors for the development of CMV infection including: use of alemtuzumab (n=9), corticosteroid therapy of ≥ 1 mg of solumedrol equivalent/kg for treatment of graft versus host disease (n=12), or unrelated donor transplant (n=12), (Table 2). Of the 12 patients with graft versus host disease (GVHD), 5 had GVHD involving the lower gastrointestinal tract.

Table 1. Patient Characteristics (N=30)

Median Age (range)	*53 (14-70)*
Source of Stem Cells	
Bone Marrow	4
Peripheral Blood	26
Type of Transplant	
Related	18
Unrelated	12
Type of Conditioning Regimen	
Ablative	17
Non-Ablative	13

Table 2. Risk Factors for CMV Infection (N=30)

Graft versus Host Disease	12
Use of Alemtuzumab	9
Unrelated Donor	12
Patients with at least one risk factor	24

Toxicity

Myelosuppression related to valganciclovir include thrombocytopenia (4) and neutropenia (1). The patient with neutropenia received granulocyte colony stimulating factor (G-CSF). An additional patient received two doses of G-CSF prior to the development of neutropenia for a WBC of 1,700/µL. None of the other 28 patients received growth factors during administration of valganciclovir. All patients restarted valganciclovir with dose adjustments after resolution of myelosuppression. In addition, 9 patients required modification in the dose of valganciclovir due to decrease in creatinine clearance. No other grade 3 or 4 toxicities related to valganciclovir were reported.

CMV infection and survival

CMV infection as measured by CMV PCR of ≥ 1000 copies/mL occurred in 4 patients. None of the patients developed CMV disease. CMV infection occurred in 2 patients during treatment of graft versus host disease and in 1 patient who received alemtuzumab as part of his conditioning regimen. The incidence of CMV infection was 3/24 in high-risk patients. CMV infection occurred 2-4 weeks after starting prophylaxis and at a median of 47 days post transplant (range 42-60 days). All four patients had resolution of their CMV infection after treatment with either an increased dose of valganciclovir at 900 mg twice daily x 10-14 days (n=2) or by replacing valganciclovir with IV ganciclovir at 5 mg/kg twice daily x 10-14 days (n=2). None of the 5 patients with gastrointestinal GVHD developed CMV infection.

Patients continued CMV prevention off protocol and per institutional standards between day +100 and 6-month post transplant. CMV prevention strategies during this period consisted of either prophylaxis with valganciclovir or preemptive therapy with either valganciclovir or IV ganciclovir. CMV infection between day +100 and 6 months post transplant was monitored in 21 patients. Of these, 4 developed CMV infection between 100 days and

6 months post transplant. Three of these patients received preemptive therapy while one developed CMV infection while on valganciclovir prophylaxis. All four patients were successfully treated with intravenous ganciclovir. Overall survival for this cohort was 93% and 63% at 100 days and 6 months post-transplant respectively. Causes of death were: relapse (n=5), graft versus host disease (n=3), sepsis (n=2) and interstitial pneumonitis (n=1) not related to CMV.

DISCUSSION

An increasing number of CMV infections occur late after allogeneic stem cell transplant (>100 days).[20] Factors associated with an increased risk of late CMV infection include: immune suppression associated with graft versus host disease, low CD4 counts, the use of donor lymphocytes, and prolonged use of ganciclovir early after allogeneic stem cell transplant.[14,20,21] Risk factors also identify a patient population at increased risk of CMV infection early after allogeneic stem cell transplant (Table 3).[12-14] The incidence of CMV infection in seropositive patients receiving alemtuzumab as part of the conditioning regimen was reported to be as high as 85% with a median time to CMV infection of 27 days.[13] Similarly the incidence of early CMV infection is high in patients developing graft versus host disease and in patients undergoing unrelated donor transplant.[12,26] Furthermore, the time to progression from viral detection to overt CMV disease is shortened in highly immunesuppressed patients.[23] Prophylactic strategies may have a role for this high risk group.

CMV prophylaxis with ganciclovir requires intravenous administration and is associated with increased toxicities related to myelosuppression. In previous studies, the severity of myelosuppression associated with ganciclovir prophylaxis varied with the schedule of administration and was reported at a time when growth factors were not routinely used. Safer and more convenient strategies for CMV prevention are under investigation. Valacyclovir is a valyl ester of acyclovir with improved bioavailability. Oral valacyclovir proved to be as effective as intravenous ganciclovir in the early prophylaxis of CMV but required the intake of 8 grams of drug per day and it appeared to be effective only in low risk patients.[21,24]

Valganciclovir, as reported in this trial was well tolerated with minimal, reversible myelosuppression. The low incidence of myelosuppression is likely related to reduced dosing and adjustments based on creatinine clearance. It could also be related to the use of peripheral blood as the source of stem cells in most study patients and the use G-CSF. Despite dose adjustments, the incidence of CMV infection was low in this small study of patients at high risk. Resistance after valganciclovir prophylaxis was not observed as all 4 patients developing CMV infection were successfully treated with IV ganciclovir or increased doses of valganciclovir. Furthermore, late CMV infection at 3 to 6 months post-transplant occurred in 4 patients and all were successfully treated with IV ganciclovir.

Recent studies have identified patients with a higher incidence of CMV infection and disease. Valganciclovir prophylaxis is an alternative for patients who are at high risk of CMV infection. Randomized, placebo controlled studies are needed to conclusively define the role of valganciclovir and other active drugs in the early prophylaxis of CMV infection and the ultimate goal of preventing CMV disease.

Table 3. Risk Factors for CMV Infection

Reference	*N*	*Risk*	*CMV Incidence (%)*
Junghaus et. al.	59	unrelated donor transplant	68
Charkarbartic, et. al.	101	Alemtuzumab	85 (CMV seropositive patients)
Miller et. al.	81	Acute GvHD	41

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