의학석사 학위논문

Efficacy of preemptive treatment with a half-dose of ganciclovir for CMV infection after pediatric allogeneic hematopoietic stem cell transplantation

소아 동종 조혈모세포이식 후 발생한 거대세포바이러스 감염에서 절반 용량 ganciclovir preemptive treatment 의 효과

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주 희 영

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Department of Clinical Medical Sciences, Graduate School,

Seoul National University College of Medicine

Hee Young Ju

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by

Hee Young Ju

A thesis submitted to the Department of Clinical Medical Sciences, Graduate School in partial fulfillment of the requirements for the Master of Science in Clinical Medical Sciences at Seoul National University College of Medicine

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Approved by Thesis Committee:

Professor _____**Chairman**

Professor _____

Professor _____

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논문 제목: Efficacy of preemptive treatment with a half-dose of ganciclovir for CMV infection after pediatric allogeneic HSCT

학위구분: **석사 ■ · 박사 □**
학 과: 임상의과학과
학 번: 2012-22728
저 작 자: 주 희 영 (인)

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서울대학교총장 귀하

ABSTRACT

Introduction: Cytomegalovirus (CMV) infection remains a major cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT). Ganciclovir has potent activity against CMV and has been used successfully to treat CMV infection in immunocompromised recipients. However, the suppression of bone marrow function associated with ganciclovir treatment has been of particular concern. We did acyclovir prevention in all patients, and preemptive treatment of CMV infection with a half-dose of ganciclovir in asymptomatic recipients of HSCT when CMV antigenemia level was under 10/200,000 cells.

Methods: Preventive acyclovir was administered at all of the HSCT patients. Patients received a preemptive half-dose of IV ganciclovir (5mg/kg once daily, 6 days a week) when CMV antigenemia had been detected at least once in less than 10/200,000 cells. If CMV antigenemia had been detected in more than or equal to 10/200,000 cells, conventional ganciclovir induction therapy (5mg/kg every 12 hours) was administered. When the CMV antigenemia was checked to be negative twice at the routine antigenemia test per 3 days, we concluded that the antigenemia was cleared and terminated the treatment.

Results: A total of 130 patients were evaluated. CMV antigenemia was detected in 87 (66.9%) patients. The median day of CMV detection was 31 (11-300) days after transplantation, and the median number of cells in CMV antigenemia was 2 (1-49)/200,000 cells. Seventy-four patients (85.1%) received preemptive treatment with a half-dose of ganciclovir. Twenty-three (31.1%) patients of those who initially received half-dose of ganciclovir needed following induction therapy because of increase in CMV antigenemia over 10/200,000 cells in spite of the preemptive treatment. In fifty-one (68.9%) patients, viral clearance was achieved which meant half dose GCV was sufficient for the treatment of CMV infection. Only two (2.7%) patient who started with half-dose ganciclovir treatment developed CMV retinitis.

Conclusions: This article conclude preemptive treatment with half-dose ganciclovir for patients

with CMV antigenemia whose level is under 10/200,000 cells could be a successful and safe approach for CMV infection after HSCT.

Keywords: Ganciclovir Preemptive treatment, Cytomegalovirus infection, allogeneic hematopoietic stem cell transplantation, pediatric

Student number: 2012-22728

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LIST OF ABBREVIATIONS

Ag : Antigenemia

ATG : Anti-thymocyte globulin

CBT : Cord blood transplantation

CMV : Cytomegalovirus

CsA : Cyclosporine

FK506 : Tacrolimus

GVHD : Graft-versus-host disease

HSCT : Hematopoietic stem cell transplantation

MMF : Mycophenolate mofetil

MTX : Methotrexate

OR : Odds ratio

OS : Overall Survival

PCR : Polymerase chain reaction

PFS : Progression-free survival

INTRODUCTION

Cytomegalovirus (CMV) infection is a major cause of morbidity and mortality following hematopoietic stem cell transplantation (HSCT). To overcome this obstacle, preventive strategies including general prophylaxis and preemptive therapy have been proposed. Acyclovir was suggested for the prophylaxis of CMV infection, but CMV was less sensitive to inhibition by acyclovir than the other herpes viruses such as herpes simplex of varicella-zoster viruses in vitro (1). Ganciclovir, more potent drug for CMV was proposed for prevention of CMV disease, but universal prophylaxis with ganciclovir could not improve the outcome because of neutropenia caused by ganciclovir (2). Therefore preemptive therapy, which initiates when CMV infection is detected, has become the standard strategy nowadays. Preemptive treatment strategy depends on the presence of CMV in the blood before the onset of disease and the early detection of CMV. At first the recommended dose of ganciclovir for preemptive treatment after allogeneic HSCT was 5mg/kg bid for 7-14 days (3). However, recent reports suggested half-dose of ganciclovir preemptive treatment in adult allogeneic HSCT patients to decrease the risk related to prolonged neutropenia. To evaluate the efficacy and safety of half-dose ganciclovir treatment in pediatric allogeneic HSCT patients, we performed retrospective analysis of the patients treated with half-dose ganciclovir treatment at a single center.

PATIENTS AND METHODS

1. Patients

This retrospective study was done by reviewing the medical record of the patients. All pediatric patients who underwent allogeneic HSCT at Seoul National University Children's Hospital between January 2009 and September 2012 were eligible for this study. Conditioning regimen and graft-versus-host disease (GVHD) prophylaxis was selected according to the disease and donor.

2. CMV antigenemia assay

The detection of CMV pp65 antigen in leukocytes was used as a diagnostic test to determine the need for preemptive treatment. CMV pp65 antigen was detected by binding monoclonal antibody (Biotest, Germany), and then staining with ultraview universal alkaline phosphatase red detection kit (Ventana, Roche). CMV antigenemia assay was performed twice per week from engraftment to 90 days after HSCT. When the antigenemia checked to be positive, quantitative CMV polymerase chain reaction (PCR) test, and evaluation for CMV retinitis was done by the ophthalmologist was done. The lower limit of detection of the CMV DNA was 100 copies/ml.

3. CMV antiviral therapy

All patients received antiviral prophylaxis with acyclovir (500mg/m2 iv q8hr) from the infusion day. The therapy was changed to oral form medication according to patient's general condition, and continued until 90 days after transplantation. Intravenous immunoglobulin (0.5g/kg/day) was administered from day -2, and per every 2 weeks until 3 months, and per 4 weeks thereafter until 6 months from HSCT.

Half-dose preemptive therapy with GCV was started at an induction dose of 5mg/kg/day (once per day, six days/week) when CMV positive cells less than 10 were detected per 200,000 cells. The dose of GCV was increased to 2*5mg/kg/day (seven days/week) when CMV positive cells were increased to 10 or more per 200,000 cells. When the CMV antigenemia was checked to be negative for two times consequently, the GCV was discontinued. (Fig. 1) The GCV dose was adjusted according to the renal function. For the patients with CMV antigenemia initially detected with level over 10/200,000 cells, GCV induction dose (2*5mg/kg/day, seven days/week) was administered. Preventive acyclovir was discontinued if the ganciclovir treatment was started.

4. Definitions

CMV infection was defined as isolation of the CMV by the CMV antigenemia study and/or culture study. Viral clearance was defined as negative conversion of CMV antigenemia. CMV pneumonia was defined by the presence of signs and/or symptoms of pulmonary disease combined with the detection of CMV in bronchoalveolar lavage fluid or lung tissue samples. Detection of CMV was confined to virus isolation, histopathologic testing, immunohistochemical analysis, or in situ hybridization. Detection of CMV by PCR alone was not sufficient for the diagnosis of CMV pneumonia. CMV gastrointestinal disease was defined by identification of a combination of clinical symptoms, findings of macroscopic mucosal lesions on endoscopy, and demonstration of CMV infection in a gastrointestinal tract biopsy specimen. CMV hepatitis was defined by findings of elevated bilirubin and/or liver enzymes, absence of any other documented cause of hepatitis, and detection of CMV infection in a liver biopsy specimen. CMV retinitis was confirmed by an ophthalmologist (4).

5. Statistical Methods

The primary endpoint of the study was the viral clearance rate and the incidence of CMV disease. The secondary endpoint of the study was the incidence of neutropenia after the half-dose preemptive treatment. Statistical analyses were performed using Stata/IC 12.0. Overall survival (OS) was calculated from the date of initial diagnosis to the date of death or last follow-up. Progression-free survival (PFS) was determined from the date of initial diagnosis to the date of progression or last follow-up. Survival was analyzed using the Kaplan–Meier method, and a Cox regression analysis was performed for OS and PFS. We carried out logistic regression analysis, and P value of <0.05 was considered to be statistically significant.

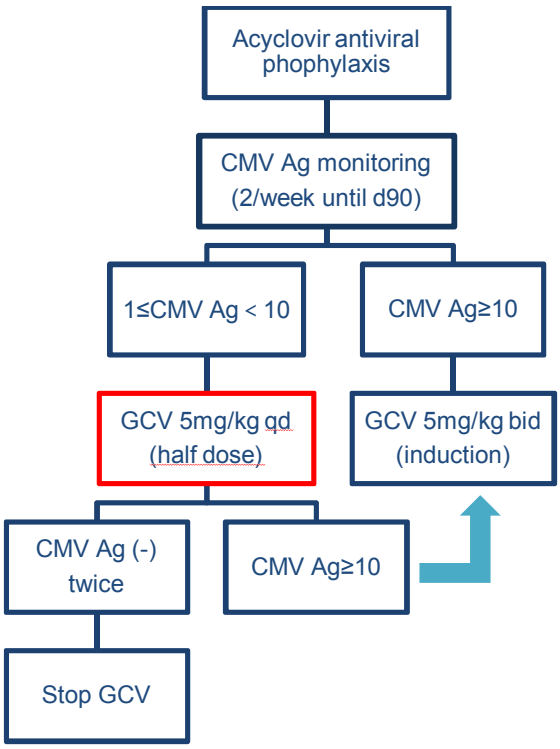

Fig. 1 Treatment scheme for CMV infection. Test for CMV viral load was performed when CMV antigenemia checked to be positive.

RESULTS

Patient characteristics

A total of 130 patients were enrolled in the study. Among these patients, 66 were male and 64 were female, and median age of the total patients was 10.0 years (range 0.1-18.7 years). Most common disease was AML (33.9%), and unrelated matched donor was the most common donor type (51.5%). One hundred and nine patients (83.8%) adopted myeloablative conditioning, 19 patients (14.6%) adopted reduced intensity conditioning, and two patients (1.5%) with severe immune combined deficiency did not use conditioning. Most of the patients (n=118, 90.8%) adopted anti-thymocyte globulin (ATG) before HSCT. Patients' characteristics are presented in Table 1.

CMV infection and half-dose preemptive therapy

CMV infection was detected in 87 patients (66.9%). Median CMV Ag level at first detection was 2/200,000 cells (range 1-49), and the median CMV viral load was 1,812 copies/mL palsma (range 0-38,578). Median CMV detection day was 31 days after HSCT (range 11-300). Seventy-four patients (85.1%) adopted GCV half-dose preemptive therapy and fifty-one (68.9%) of them obtained viral clearance. Other twenty-three (31.1%) patients underwent following induction ganciclovir therapy after the half-dose therapy due to elevation of CMV Ag level during treatment. Nevertheless the ganciclovir treatment, two patients developed CMV retinitis, and both were treated successfully. In contrast, among the 10 patients who were treated with ganciclovir induction therapy initially, three CMV disease patients (30%) developed CMV disease.

There were three patients who showed CMV Ag level under 10 but did not undergo ganciclovir treatment. This was because the abnormal CMV Ag lab result was not detected, and

when positive atigenemia was detected the next lab turned to be negative. These three patients showed spontaneous regression of CMV antigenemia.

Relapse of CMV infection developed in 14 patients after half-dose ganciclovir treatment-only patients (18.9%), 15 patients who underwent induction therapy after half-dose ganciclovir treatment (65.2%), and 4 patients who started with ganciclovir induction therapt directly (40%), respectively. This indicate that patients who needed further induction ganciclovir treatment after the half-dose treatment showed more frequent relapse.

When the recipient was CMV seropositive, the risk of CMV infection was increased (OR 11.03, P=0.049). Other factors as presence of acute GVHD, usage of ATG, donor CMV serology was not related to the occurrence of CMV infection. Among the patients with detected CMV infection, 29 patients (33.3%) were using methylprednisoline over 0.5mg/kg/day when CMV infection was detected. However, the usage of methylprednisolone was not a significant factor related to the development of CMV infection or disease.

CMV disease

Four patients developed CMV disease, which were all retinitis. One patient with CMV retinitis was successfully treated for the CMV disease, but relapsed acute lymphoblastic leukemia thereafter and died bacuse of disease progression. Other three patients are alive without evidence of disease. There was no death related to CMV disease.

In our study, occurrence of CMV disease was not related with type of transplantation, type of conditioning regimen, usage of ATG, GVHD prophylaxis medication, and usage of methlyprednisolone (0.5mg/kg/day or more). There was a trend of higher CMV disease when the patient had acute GVHD, but was not statistically significant (OR 7.905, P=0.068).

Adverse events during half-dose preemptive therapy

Neutropenia, which was defnied as neutrophil count under 1,000/μl, occurred in 70% of induction dose ganciclovir-treated patients, and 56.8% of half-dose ganciclovir-treated patients. The rate was higher in induction treatment patients, but there was no statistically significant difference between two groups.

Additionally, analysis was done for the five patients who died of severe infection within three months from the initiation of ganciclovir treatment. Among them, two patients performed ganciclovir induction treatment only, and three patients underwent induction treatment after half-dose of preemptive ganciclovir treatment. There was no patient who died of severe infection after half-dose preemptive dose ganciclovir treatment only.

Survival, TRM

Overall survival (OS) of the patients with CMV infection were 75.6%, and OS of the patients without CMV infection were 78.4%. (Fig. 3) The OS was not related with CMV infection, CMV Ag level, CMV viral load, or CMV disease.

Table 1. Patient characteristics.

	Total patients		CMV infection
	Number (N=130)	%	Yes (N=88)
Median age (range)	10.0	(0.1-18.7)	
Sex			
Male	66	50.8%	43 (65.2%)
Female	64	49.2%	44 (68.8%)
Disease			
Acute lymphoblastic leukemia	41	31.5%	29 (70.7%)
Acute myeloid leukemia	44	33.9%	25 (56.8%)
Acute biphenotypic leukemia	7	5.4%	6 (85.7%)
Severe aplastic anemia	16	12.3%	11 (68.8%)
Myelodysplastic syndrome	3	2.3%	3 (100%)
Others	19	14.6%	13 (68.4%)
Conditioning Regimen			
Myeloablative conditioning	109	83.8%	72 (66.1%)
Reduced intensity conditioning	19	14.6%	14 (73.7%)
Not done	2	1.5%	1 (50%)
Donor source			
Matched related	36	27.7%	26 (72.2%)
Unrelated	67	51.5%	43 (64.2%)
Cord blood	22	16.9%	14 (63.6%)
Mismatched related	5	3.8%	4 (80%)
Anti-thymocyte globulin treatment			
Received	118	90.8%	78 (66.1%)
Not received	12	9.2%	9 (75%)
GVHD prophylaxis			
CsA+Pd	42	32.3%	31 (73.8%)
CsA+MMF	22	16.9%	15 (68.2%)
FK506+MTX	63	48.5%	40 (58.8%)
Others	1	0.8%	0 (0%)
None	2	1.5%	1 (50%)
Recipient / Donor CMV serostatus*			
Positive / Positive	88	67.7%	63 (71.6%)
Negative / Positive	15	11.5%	9 (60%)
Positive / Negative	3	2.3%	1 (33.3%)
Negative / Negative	1	0.8%	0 (0%)

Abbreviation: CMV, cytomegalovirus; CsA, cyclosporine A; Pd, prednisolone; MMF, mycophenolate mofetil

* Patients receiving cord blood transplantation was excluded from serostatus.

Table 2. Univariate and multivariate analyses for the development of CMV antigenemia

	Univariate		Multivariate	
Characteristics	HR (95% CI)	*P*	HR (95% CI)	*P*
Age group, years				
≥ 10 (vs. < 10)	1.42 (0.68–2.95)	0.352	1.47 (0.63–3.39)	0.371
Sex				
Male (vs. Female)	0.85 (0.41–1.77)	0.663	0.78 (0.35–1.72)	0.534
Conditioning				
Myeloablative (vs. reduced intensity)	0.75 (0.24–2.36)	0.619	0.81 (0.25–2.60)	0.722
Anti-thymocyte globulin treatment				
Received (vs. not received)	0.62 (0.08–4.64)	0.646	0.47 (0.08–2.82)	0.412
Donor source				
Related (vs. unrelated)	1.41 (0.61–3.27)	0.428	1.22 (0.38–3.86)	0.738
Graft-versus-host disease prophylaxis				
CsA-based (vs. non-CsA)	1.47 (0.70–3.11)	0.313	1.25 (0.45–3.46)	0.674
Recipient CMV serostatus				
Positive (vs. negative)	8.82 (0.95–81.52)	0.055	11.03 (1.01–120.68)	0.049

Abbreviation: HR, hazard ratio; CI, confidence interval; CMV, cytomegalovirus; CsA, cyclosporin

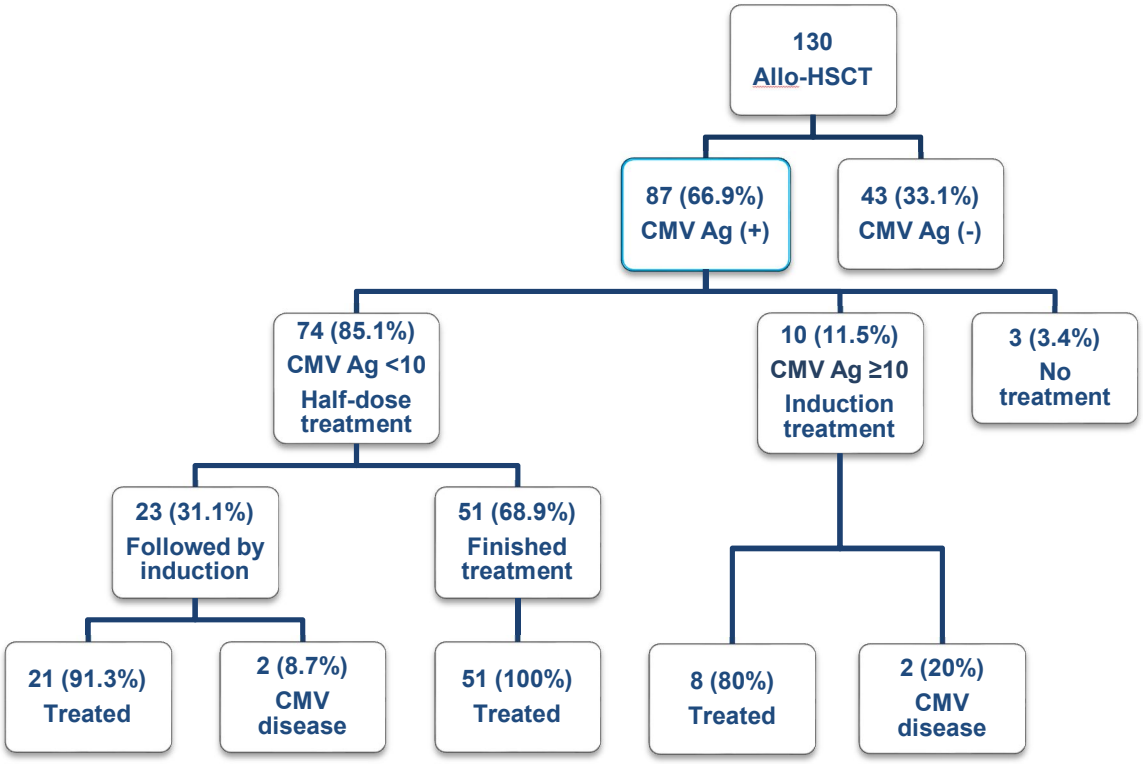

Fig. 2 Treatment results of CMV infection patients.

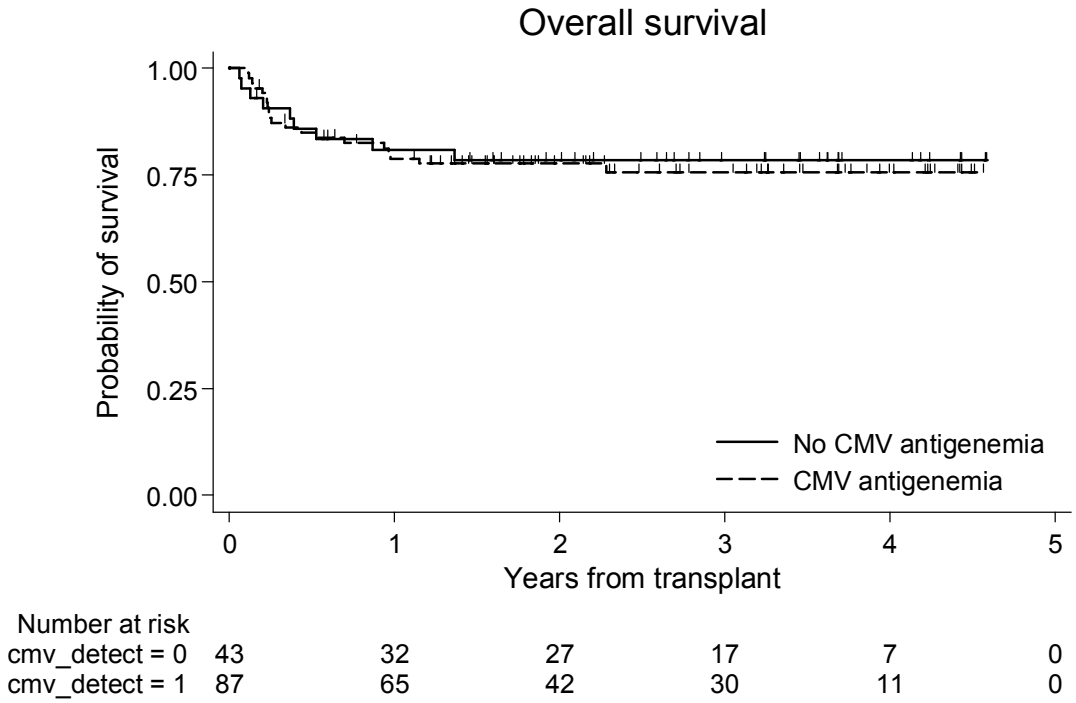

Fig. 3 Overall survival (OS) of patients with CMV infection were 75.6%, and OS of patients without CMV infection were 78.4%.

DISCUSSION

Recent adult HSCT studies showed promising result of half-dose of ganciclovir preemptive treatment for CMV infection (5-9), but there have been no pediatric studies for half-dose ganciclovir treatment yet. Most recent case-control study showed that the low-dose ganciclovir preemptive therapy was not inferior to conventional dose ganciclovir therapy in adults (5). In current study, we performed the acyclovir preventive strategy together with half-dose ganciclovir preemptive treatment. The importance of this study is that half-dose ganciclovir preemptive therapy was done in pediatric HSCT patients, and the efficacy and safety was predictable. Recent pediatric study about viral reactivation showed that preventive acyclovir (3x15mg/kg for seropositive patients) with preemptive ganciclovir therapy (2x5mg/kg/day) resulted in 28% of CMV reactivation, and 50% of those patients developed CMV disease (10). Relatively high incidence of CMV reactivation in our study may be because of lower dose of acyclovir, and predominance of CMV seropositivity; 99.2% of HSCT were recipient or donor, or both CMV seropositive. However, CMV disease occurrence was much lesser in current study (5.7% of CMV reactivation patients), showing the superiority of this strategy. Although there was one patient in current study who was detected CMV antigenemia at 300 days after HSCT, all the other patients was diagnosed CMV infection between 11 to 67 days after HSCT. Previous studies have performed 6 months of duration for acyclovir preventive strategy (11), but we suggest that 90 days of prevention could be sufficient for prevention of CMV disease when combined with the half-dose ganciclovir preemptive treatment.

The positive CMV serostatus of the recipient was an important factor for predicting the occurrence of CMV infection, accordant with previous results (10). But the CMV serostatus did not influence the CMV disease occurrence. And the treatment response to ganciclovir half-dose preemptive therapy, based on viral clearance rate, was not different between seropositive and seronegative patients. Thus the positive CMV serostatus of the recipient is a risk factor for

CMV infection, but it is not needed to specify the preemptive treatment for CMV seropositive patients. However, there can be a bias because of the high seropositive rate in our study; there was only one HSCT whose donor and recipient were both seronegative. Furthermore, patients who did not complete the MMR (mumps, measles, rubella) vaccination were provided prophylactic immunoglobulin, and this could be the factor which interacted the CMV serostatus.

At previous studies, presence of acute GVHD, high dose steroid treatment, T cell depletion, and cord blood transplantation was proved to be related to higher risk of CMV disease (5, 12, 13). But there was no factor among these associated with the occurrence of CMV disease in our study. This may be owing to the small number of CMV disease patients in our study. Previous reports showed the risk of CMV infection was elevated when the anti-thymocyte globulin (ATG) was used, but we could not prove it in this study. This may be due to the preponderance usage of ATG in our study, or due to the adjustment of ATG dose and administration time according to disease and type of transplantation.

In our study, CMV viral load was not routinely monitored but was checked once when CMV infection was detected by pp65 antigenemia study, before the initiation of ganciclovir treatment. The initial viral load was variable, which was distributed from 0 to 38,578 copies/mL. There was a tendency of increasing CMV viral load with CMV antigenemia level. (Fig. 4) There were six patients who showed CMV antigenemia level as 1/200,000 cells, but presented viral load as 0 copies/mL. All of them were treated successfully with only the half-dose preemptive ganciclovir. This indicates that if a patient shows negative CMV viral load test, there is low risk of CMV disease. Thus if the patient's CMV viral load results to be zero, it would be reasonable to consider early discontinuation of the ganciclovir treatment although the CMV antigenemia showed to be positive. The absolute value of initial CMV viral load itself was not sufficient for further prediction for CMV disease or survival in our study. Recent studies showed the predictability of CMV viral load (14-16), supported by the sensitivity and quantitative nature of

the test. But there are still several variations in assay performance and testing material, making it difficult to establish validated universal viral load thresholds (17).

There was no difference of CMV disease rate and OS between the three patients who were not treated but showed spontaneous regression of CMV antigenemia, and the patients who were treated immediately. This may indicate that the treatment can be delayed until antigenemia level elevation or if the antigenemia is checked positive for two times sequentially. For the confirmation of this hypothesis, we tried to classify the risk patients according to the CMV antigenemia value. However, it was impossible to prove the difference of CMV disease risk between groups classified by CMV antigenemia value of 2 or 5. Recent adult study suggested the threshold for GCV preemptive treatment as CMV antigenemia of ≥ 5/200,000 cells for high risk patients and ≥ 20/200,000 cells in low risk patients (5). Furthermore, the trend is moving to stricter threshold of CMV Ag level for starting the ganciclovir treatment. Most recent study reported 20 positive cells for starting preemptive study was not associated with significant increase of CMV disease in low risk patients (18). However from our study result, grading according to Ag level was not meaningful.

Previously, ganciclovir-related neutropenia was described as a dose-dependent inhibition of DNA-polymerase in hematopoietic cells (19). In our study, neutropenia after ganciclovir treatment showed higher rate in induction-ganciclovir treated patients, but the difference was not statistically significant. However, the fact that no patient died of severe infection after half-dose preemptive dose ganciclovir treatment proves the safety of half-dose ganciclovir treatment, indirectly.

In conclusion, gangicovir half-dose preemptive treatment was safe and efficient in CMV

infection of pediatric allogeneic HSCT patients. The half-dose ganciclovir treatment was sufficient for 68.9% of the patients, and the CMV disease was not increased, and no death related to CMV disease occurred. There was no severe infection related to neutropenia after half-dose of ganciclovir treatment. The risk of CMV infection was elevated in CMV seropositive recipients, but the CMV disease was not related with serostatus. The treatment response was not different according to initial CMV antigenemia level or viral load. On the basis of this study result, we suggest that preventive acyclovir with half-dose ganciclovir preemptive therapy could substitute the conventional preemptive therapy at patients with CMV Ag level below 10. These results should be proved by a prospective study.

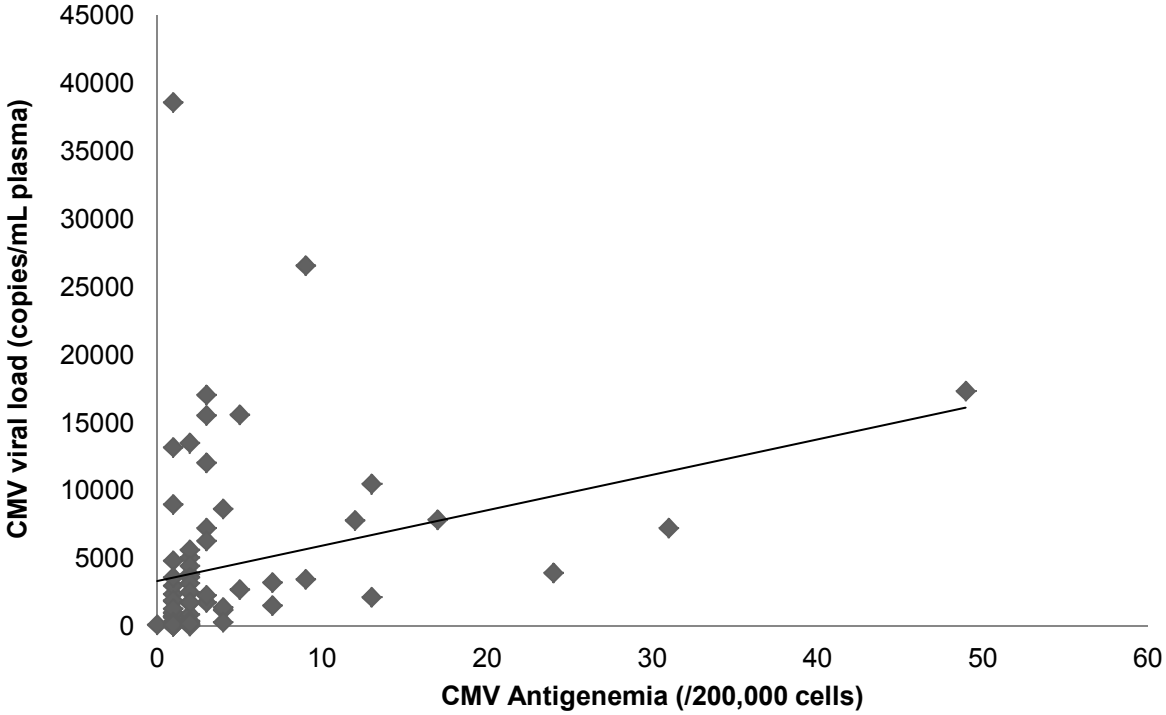

Fig. 4 Relation of CMV antigenemia level and CMV viral load.

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국문 초록

서론: 거대세포바이러스 감염은 조혈모세포이식 이후 사망 및 합병증의 중요한 부분을 차지하는 질환이다. 이식 후 거대세포바이러스로 인한 질환의 예방을 위해서는 ganciclovir preemptive therapy 가 주로 이용되는데, 이는 예방적 효과도 있지만 약제 부작용으로 중성구감소증이 발생할 수 있어 최근에는 용량을 감량한 치료가 제시되고 있다.

방법: 본 논문에서는 ganciclovir preemptive therapy 를 과거에 비하여 절반 용량으로 치료한 소아 동종조혈모세포 이식 환자들에서 치료 성적 및 안전성에 대하여 후향적으로 분석하였다. 환자들은 동종 조혈모세포이식 이후 거대세포바이러스 pp65 항원에 대해 2회/주로 검사하여서 그 값이 10/200,000 세포 미만으로 양성이 확인된 경우 절반 용량의 ganciclovir (5mg/kg/dose, 1회/일로 6일/주)를 투약하였다.

결과: 2009년 1월부터 2012년 9월까지 서울대학교 어린이병원 소아청소년과에서 동종 조혈모세포 이식을 시행받은 환자들 130 명 중 87명 (66.9%)에서 거대세포바이러스 감염이 확인되었으며, 이중 74명 (85.1%)에서는 절반 용량 ganciclovir preemptive therapy 가 시행되었다. 이들 중 23 명 (31.1%)에서는 치료 중 거대세포바이러스 항원의 증가로 인해 ganciclovir 관해 치료가 시행되었고, 51명 (68.9%)에서는 절반 용량 ganciclovir preemptive therapy 로 치료가 종료되었다. 절반 용량 ganciclovir preemptive therapy로 치료를 시작한 환자 중 2명 (2.7%) 에서 거대세포바이러스 망막염이 발생하였으나 성공적으로 치료되었다.

결론: 본 논문의 저자들은 절반 용량 ganciclovir preemptive therapy 이 거대세포바이러스 항원 10/200,000 세포 이하로 발견되는 소아 동종조혈모세포이식 환자들에서 효과적이고 안전한 치료법으로 평가한다.

주요어 : 거대세포바이러스, 간싸이클로비어 예방적치료, 동종조혈모세포이식, 소아

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