Journal of Microbiology, Immunology and Infection (2011) 44, 442—448

available at www.sciencedirect.com

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journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Risk factors and outcomes of cytomegalovirus viremia in cancer patients: A study from a medical center in northern Taiwan

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Received 10 May 2010; received in revised form 10 October 2010; accepted 22 December 2010

KEYWORDS
Cancer;
Cytomegalovirus;
Polymerase chain reaction;
Pre-emptive therapy;
Viremia

Background: Cytomegalovirus (CMV) is a pathogen and can cause life-threatening infection in the patients with malignancies. This study was conducted to investigate the risk factors and outcomes of CMV viremia in patients with malignancies.
Methods: Data were collected with retrospective analysis from adults suffering from CMV viremia with underlying malignancies. A total of 107 patients were enrolled in a tertiary medical center in northern Taiwan from March 2008 to December 2009.
Results: Among the 107 patients who suffered with CMV viremia with an overall mortality rate of 56.1% (60/107), 75 patients (70.1%) had solid organ malignancies and 32 (29.9%) had hematological malignancies. Mechanical ventilation ($p = 0.048$), leukocytosis ($p = 0.004$), and lack of appropriate early treatment ($p = 0.011$) were independent predisposing factors associated with higher mortality rate.
Conclusions: CMV viremia predicts high mortality rate in cancer patients, especially in those with mechanical ventilation, leukocytosis, and lack of appropriate early treatment. Appropriate early antiviral therapy is recommended to improve outcomes.

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1684-1182/$36
doi:10.1016/j.jmii.2011.04.004

Introduction

Cytomegalovirus (CMV) is an important cause of both morbidity and mortality in immunocompromised hosts, including cancer patients.[1–3] Patients with CMV infection have a wide variety of clinical manifestations, including fever, encephalitis, pneumonitis, retinitis, hepatitis, enterocolitis, nephritis, and disseminated disease.[4–7] The exact mechanism of the reactivation of CMV is not well established; however, disturbance of the host's immune defenses plays an important role.[8–10] Immune impairment in the patients with malignancies was considered to be a risk factor for CMV disease.[9,10] The term "CMV infection" indicates latent and asymptomatic form of infection,[9] whereas the "CMV disease" means the symptomatic end-organ involvement.[9] The incidence of CMV infection in patients with malignancies varies in different studies.[11–13]

Several tests, such as viral culture, antigenemia assay, and polymerase chain reaction (PCR) were used for the diagnosis of CMV infection.[9,10,14,15] Of all the laboratory tests, PCR is the most sensitive and rapid method for early diagnosis.[14,15] Both "prophylaxis" and the "pre-emptive treatment" have been proposed as the therapeutic strategies.[9,16] The "pre-emptive therapy" was defined as antiviral therapy given for the laboratory evidence of viral replication (detected by viral culture, antigenemia, and PCR). In Taiwan, there are limited clinical data of the patients suffering with CMV infection accompanied with malignancies. Thus, we conducted this study to elucidate the risk factors and outcomes in these patients.

Methods

Study design

The clinical and microbiological data we retrospectively evaluated were the cases of CMV viremia in Tri-Service General Hospital from March 2008 to December 2009. Only patients with solid organ malignancies or hematological malignancies were enrolled. Patients either infected with human immunodeficiency virus or who received solid organ or bone marrow transplantation were excluded.

Patient enrollment and data collection

Information of patients enrolled in the study was obtained from the medical records, including demographic characteristics, predisposing factors, comorbid conditions, laboratory data, and treatment outcomes.

PCR

We used two sets of primers, one specific for CMV and the other specific for human DNA. The CMV primers were directed at a conserved region of the DNA polymerase gene of strain AD169. The nucleotide sequence were 5′-GCT GAC GCG TTT GGT CAT C-3′ (CPOL-F720) for the forward primer and 5′-ACG ATT CAC GGA GCA CCA G-3′ (CPOL-R780) for the reverse primer. The internal probe (CPOL-741FAM), 5′-TCG GCG GAT CAC CAC GTT CG, was labeled at the 5′ end with the fluorescent dye 6-carboxyfluorescein and on the 3′ end with the quencher dye 6-carboxytetramethylrhodamine (TETRA). The real-time, quantitative CMV PCR assay did not amplify laboratory strains of any of the other seven human herpes viruses.[14]

Definitions

We used the real-time PCR assay for the diagnosis of the infection. Positive result of CMV-specific real-time PCR assay in serum was defined as CMV viremia. Exposure to chemotherapy was defined as receiving chemotherapeutic agents within 1 week before the diagnosis of CMV viremia. Coinfection was defined as the presence of other microorganisms identified from the blood simultaneously with CMV. Laboratory data obtained within 7 days before the diagnosis of CMV viremia were analyzed. Leukocytosis was defined as a leukocyte count of more than 10,000 cells/μL and leukopenia was defined as a leukocyte count of less than 4,000 cells/μL. Neutropenia was defined as an absolute neutrophil count less than 500 cells/μL or less than 1,000 cells/μL with a predicted nadir of less than 500 cells/μL. Lymphopenia was defined as an absolute lymphocyte count of less than 1,000 cells/μL. Antiviral therapy started within 3 days of the diagnosis and lasted at least 3 days was considered to be appropriate early treatment. The overall mortality was defined as fatality within 30 days of the emergence of viremia.

Statistical analysis

All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) for windows (Version 17.0; SPSS, Chicago, IL, USA). Continuous variables were analyzed by unpaired Student t test. Comparisons between categorical variables were calculated using the Pearson χ^2 test or Fisher's exact tests. Univariate analysis was performed to demonstrate the association between potential risk factors and overall mortality associated with CMV viremia. Multiple logistic regression analysis was conducted to determine the independent risk factor for mortality associated with CMV viremia. Odds ratios and 95% confidential intervals were calculated to evaluate the strength of any association and estimate the effect in the outcome analysis. A p value less than 0.05 was considered to be statistically significant.

Results

During the 22-month study period, 107 patients with positive result of CMV-specific PCR were enrolled. The demographics, predisposing factors, comorbid conditions, and the laboratory data are listed in Table 1. The mean ± standard deviation age of the patients was 65.6 ± 15.8 years (range 26—100 years) and the male to female ratio was 1.89 (70 men and 37 women). Sixty-two patients (66.34%) were exposed to chemotherapeutic agents within 1 week before the diagnosis of viremia. Twenty-seven patients (28.89%) had received steroids before the viremia. Diabetes mellitus was the most common comorbidity ($n = 33$; 30.8%) followed by congestive heart failure ($n = 17$; 15.9%) and liver cirrhosis ($n = 18$; 9.0%). Thirty patients (28%) received appropriate early treatment, whereas the other 77 patients (72%) did not have adequate

Table 1 Demographics, predisposing factors, and treatment outcomes for *cytomegalovirus* viremic patients with underlying solid organ malignancy and hematological malignancy

Variables	All patients ($n = 107$)	Solid organ malignancy group ($n = 75$)	Hematological malignancy group ($n = 32$)	p[a]
Age (yr)	65.6 ± 15.8	63 ± 16.6	71.8 ± 11.9	0.003
Sex				
Men	70 (65.4)	49 (65.3)	21 (65.6)	0.977
Women	37 (34.6)	26 (34.7)	11 (34.4)	
Comorbid conditions				
Congestive heart failure	17 (15.9)	13 (17.3)	4 (12.5)	0.531
Liver cirrhosis	4 (3.7)	4 (5.3)	0 (0)	0.183
Chronic obstructive lung disease	5 (4.7)	3 (4)	2 (6.3)	0.614
Diabetes	33 (30.8)	21 (28)	12 (37.5)	0.330
Rheumatological disease	4 (3.7)	3 (4)	1 (3.1)	0.827
Renal failure	5 (4.7)	4 (5.3)	1 (3.1)	0.620
Predisposing factors				
Receipt of chemotherapy	62 (57.9)	45 (60)	17 (53.1)	0.510
Use of corticosteroids	27 (25.2)	16 (21.3)	11 (34.4)	0.155
Mechanical ventilation	35 (32.7)	27 (36)	8 (25)	0.267
Coinfection	21 (19.6)	12 (16)	9 (28.1)	0.148
Presentations				
Leukocytosis	35 (32.7)	30 (40)	5 (15.6)	0.014
Neutropenia	21 (19.6)	8 (10.7)	13 (40.6)	<0.001
Lymphopenia	90 (84.1)	63 (84)	24 (84.4)	0.961
Treatment and outcomes				
Lack of early appropriate treatment	77 (72)	56 (74.7)	21 (65.6)	0.340
Mortality	60 (56.1)	46 (61.3)	14 (43.8)[a]	0.093

[a] Comparison between patients with solid organ and hematological malignancy by univariate analysis.
Data are presented as n (%) or mean ± SD.
SD = standard deviation.

early treatment. Ten patients did not receive any treatment throughout the course of the infection. Seven of them died because of mortality before the diagnosis. Intravenous ganciclovir was the only antiviral agent used in this study. Sixty patients died in this study, accounting for an overall mortality rate of 56.1%.

Comparison of the demographics, comorbid conditions, and clinical outcomes of patients with solid organ malignancies and hematological malignancies are summarized in Table 1. Seventy-five patients (70.1%) had solid organ malignancies and the 32 patients (29.9%) had hematological malignancies. The mean age of patients with solid organ malignancies was younger than those with hematological malignancies (63.0 *vs.* 71.8; $p = 0.03$). No statistical difference was noted in comorbid conditions between both groups. The mortality rates in patients with solid organ malignancies were higher than those with hematological malignancies (61.3% *vs.* 43.8%) without statistical significance specifically ($p = 0.093$).

The underlying malignancies of the 107 patients are shown in Table 2. In solid organ malignancies group, lung cancer was the most common (31/75; 41.3%), followed by colorectal cancer (7/75; 9.3%), breast cancer (6/75; 8%), and oral cavity cancer (6/75; 8%). One patient had synchronous malignancies of lung cancer and breast cancer. Only three kinds of hematological malignancies were found in the hematological group, including lymphoma, multiple myeloma, and acute lymphoblastic leukemia. Lymphoma was the most common hematological malignancy in this study accounting for more than one-half of the malignancies (26/32; 81.3%).

Twenty-one patients had coinfection with either bacteremia or fungemia (Table 3). The overall mortality rate in patients with coinfection was 52.4% ($n = 11$) without statistical significance. In patients who had coinfection with other microbes, *Candida albicans* fungemia (6/21; 28.6%) and *Klebsiella pneumoniae* (5/21; 23.8%) were the most common, followed by *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (3/21; 14.3%). One patient having coinfection of Methicillin-resistant *S aureus* bacteremia and candidemia died despite the treatment. The overall mortality associated with CMV viremia was 56.1% (60/107).

Univariant analysis showed that without exposure to chemotherapy before the viremia ($p = 0.024$), mechanical ventilation ($p = 0.010$), leukocytosis ($p = 0.003$), hypoalbuminemia (< 3 g/dl) ($p = 0.002$), and lack of appropriate early treatment ($p = 0.039$) were associated with higher mortality (Table 4). In the multivariate analysis, mechanical ventilation ($p = 0.048$; 95% confidence interval = 1.012−10.489; odds ratio = 3.259), leukocytosis

Table 2 Underlying malignancies in 107 patients with cytomegalovirus infection ($n = 107$)

Underlying malignancy	*n*
Solid organ malignancy	75
Lung cancer	31
Colorectal cancer	7
Breast cancer	6
Oral cavity cancer	6
Hepatocellular carcinoma	4
Bladder cancer	2
Cervix cancer	2
Cholangiocarcinoma	2
Esophageal cancer	2
Nasopharyngeal carcinoma	2
Prostate cancer	2
Renal cell carcinoma	2
Duodenal cancer	1
Gastric cancer	1
Glioblastoma multiforme	1
Melanoma	1
Pancreas cancer	1
Plantar cancer	1
Synchronous malignancy	1
Hematological malignancy	32
Lymphoma	26
Multiple myeloma	5
Leukemia	1
Total	107

($p = 0.004$; 95% confidence interval = 1.831−25.663; odds ratio = 6.885), and the lack of appropriate antiviral therapy ($p = 0.011$; 95% confidence interval = 1.451−18.095; odds ratio = 5.124) were independent risk factors for mortality associated with CMV viremia in cancer patients.

Discussion

CMV, belonging to herpes virus, is an important pathogen to human. After initiation, the CMV establishes lifelong or persistent infection in the host.[15,16] It may reactivate and produce consistently infectious virions that exist in the saliva, urine, and other body fluids.[15,16] Reactivation of CMV infection has been observed in patients with liver cirrhosis, sepsis, following trauma, critically ill condition, and impaired immune response, such as post-transplantation of organs and human immunodeficiency virus infection.[8,10,16–19] Patients with solid organ or hematological malignancies were thought to have impaired immunities and high risk of opportunistic infection, including the CMV infection.[1–3,12,20–22] In the absence of effective antiviral prophylaxis, the incidence of CMV infection ranges from 5% to 75% among patients with hematological malignancies.[21] An early prospective surveillance study reported the incidence of CMV infection in patients with acute leukemia that ranged from 32% to 58%.[3,20–24] However, the true incidence and consequences of viral infections for cancer patients were poorly identified.

Table 3 Concurrent pathogens in 21 patients with coinfection with other microorganisms ($n = 22$)

Pathogen	Number of isolates
Bacteria	16
Klebsiella pneumoniae	5
Pseudomonas aeruginosa	3
Methicillin-resistant *Staphylococcus aureus*[a]	3
Escherichia coli	2
Enterobacter cloacae	2
Serratia marcescens	1
Fungus	6
Candida albicans[a]	6
Total	22

[a] One patient had co-infection with *Methicillin-resistant Staphylococcus aureus* and Candida albicans.

Diagnostic tests for CMV infections include viral culture, antigen detection, PCR, and even serological and histopathological methods.[10,11,14,15] Of all, the real-time PCR is the most sensitive and rapid assay for the diagnosis of the infection.[9,10,14,15] The high sensitivity and negative predict value make it an important method for the early diagnosis of the infection.[9,10,14,15] Despite the low positive predict value for recognizing clinically significant infection, PCR remains crucial in the early diagnosis of the disease.

Ganciclovir and foscavir are the drugs of choice in the treatment for CMV infection. Three major therapeutic strategies are used for managing CMV infection, namely prophylaxis, pre-emptive treatment, and treatment for established diseases. Although prophylaxis is used for early prevention of CMV infection, the treatment of established disease is applied in patients with well-identified end-organ diseases. The pre-emptive therapy was first documented in the 1990s as a means of reducing of CMV disease.[9,10,25] This strategy has the advantage for early treatment for preventing the progression to end-organ diseases, reducing the exposure to antiviral toxicity, and maximizing the cost-benefit ratio.[9,25–27]

No previous study was conducted for analyzing the mortality rate of CMV viremia in solid organ malignancies. The overall mortality rate in this study was 56.1% (60/107). Worse outcome was found in patients with solid organ malignancies (61.3%) than those with hematological malignancies. The mortality rate in patients with hematological malignancies was 43.8% (14/32), which was compatible with previous studies with the mortality rate ranging from 30% to 57%.[4] In the multivariate analysis, leukocytosis ($p = 0.008$), mechanical ventilation ($p = 0.011$), and the lack of appropriate antiviral therapy ($p = 0.100$) were independent risk factors for mortality associated with CMV viremia. The results of our study indicated that CMV viremia in cancer patients had poor outcomes.

Leukocytosis or leukopenia is a criteria for systemic inflammatory response syndrome.[28] Both leukocytosis and leukopenia have a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Previous studies of CMV pneumonia in patients with lymphoma showed that APACHE II score of more than 16 were poor prognostic factors.[24] Our study demonstrated that leukocytosis was a predictable factor for worse outcome. This may be able to explain the fact that patients with leukocytosis had higher

Table 4 Risk factors for mortality in patients with cytomegalovirus infection ($n = 107$)

Variable	Mortality, *n* (%)	Univariate *p*	Multivariate	
			Odds ratio (95% confidence interval)	*p*
Demographic characteristics				
Sex				
Men ($n = 70$)	40/70 (57.1)	0.760		
Women ($n = 37$)	20/37 (54.0)			
Age (yr)				
≥65 ($n = 58$)	35/58 (60.3)	0.334		
<65 ($n = 49$)	25/49 (51.0)			
Underlying malignancy				
Solid organ malignancy ($n = 75$)	46/75 (61.3)	0.093		
Hematological malignancy ($n = 32$)	14/32 (43.8)			
Comorbid conditions				
Heart failure ($n = 17$)	12/17 (70.6)	0.195		
Liver cirrhosis ($n = 4$)	3/4 (75.0)	0.450		
Chronic obstructive lung disease ($n = 5$)	3/5 (60.0)	0.856		
Diabetes ($n = 33$)	17/33 (51.5)	0.526		
Rheumatological disease ($n = 4$)	1/4 (25.0)	0.235		
Renal failure ($n = 5$)	3/5 (60.0)	0.856		
Predisposing factors				
Receipt of chemotherapy ($n = 62$)	29/62 (46.8)	0.024	1.881 (0.630–5.617)	0.258
Yes ($n = 62$)	29/62 (46.8)	0.023		
No ($n = 45$)	31/45 (68.9)			
Use of corticosteroids ($n = 27$)	13/27 (48.1)	0.339		
Mechanical ventilation ($n = 35$)	26/35 (74.3)	0.010	3.259 (1.012–10.489)	0.048
Coinfection ($n = 21$)	11/21 (52.4)	0.740		
Presentations				
Leukocytosis ($n = 35$)	27/35 (77.1)	0.003	6.855 (1.831–25.663)	0.004
Neutropenia ($n = 21$)	10/21 (47.6)	0.386	1.489 (0.396–5.594)	0.556
Lymphopenia ($n = 90$)	52/90 (57.8)	0.416	2.543 (0.533–12.139)	0.242
Hypoalbuminemia ($n = 60$)	40/60 (66.7)	0.002	3.081 (1.451–18.095)	0.067
Treatment				
Early appropriate treatment				
No ($n = 77$)	48/77 (62.3)	0.039	4.001 (1.398–11.448)	0.010
Yes ($n = 30$)	12/30 (40.0)			

APACHE II score and worse outcomes. Several studies had demonstrated diverse relationship between the lymphopenia and mortality.[20,24] The differences between these studies may result from diverse populations and variant therapeutic regimens. Further studies are needed to elucidate the relationship between lymphopenia and CMV-associated fatality.

Severe sepsis is defined as patients with sepsis associated with dysfunction of organs distant from the site of infection, including the respiratory failure.[28] The estimated mortality rate in patients with sepsis ranges from 20% to 50% and approaches 70% in those with multiple organs failure.[29] It is reasonable that acute respiratory failure is a poor prognostic factor in infection. Several studies demonstrated that CMV infection caused higher mortality rate in patients with mechanical ventilation.[18,30,31] Our study also showed the mortality was higher in patients with mechanical ventilation (74.3% *vs.* 47.2%; $p = 0.008$). Other studies had demonstrated the correlations between the CMV infection and mechanical ventilation.[18,30,31] In immunocompetent patients with mechanical ventilation, the incidence of CMV infection is raised.[18,30,31] CMV infection itself may deteriorate the disease and prolong mechanical ventilation and hospital stay.[18,30,31]

Both CMV infection and respiratory failure with mechanical ventilation influenced each other and made it a more challenge to the physicians.

Only 30 patients (28%) in our study who received appropriate antiviral agents for more than 3-day duration within 72 hours of infection diagnosis were considered to have appropriate early treatment. Among them, 18 (60%) patients survived under the antiviral treatment and the others 12 (40%) died. Seventy-seven patients (72%) did not receive early antiviral treatment. Forty-eight of the 77 patients died, accounting for a crude mortality rate of 62.3%. Ten patients did not receive any antiviral agent throughout the course of infection. Seven of them died before confirmation of the diagnosis. Interestingly, the other three patients survived for more than 1 month without any treatment. That could be explained by the fact that CMV viremia did not indicate the CMV disease. However, patients without appropriate antiviral therapy had a higher mortality rate than those with appropriate antiviral therapy (62.3% *vs.* 40%; $p = 0.039$). The result indicated that pre-emptive treatment is recommended for better survival.

Several limitations of our study deserved to be acknowledged. First, we observed substantial heterogeneity among study populations. The risk factors in patients with solid organ malignancies may differ from hematological malignancies. Besides, there are a variety of malignancies in this study. The prognosis in each kind of malignancy may differ from each other. Second, the diverse stages of malignancy may be associated with different outcomes. The nature course of the disease is worse in late stage than early stage. Third, the CMV viral load, which was not available in our study, may be a significant variable in the outcome. Finally, this is a retrospective study with limitations intrinsically.

In conclusion, the overall mortality rate of CMV viremia in patients with malignancies was very high. On the basis of our study, predictors of death associated with CMV viremia in patients with malignancies included leukocytosis, mechanical ventilation, and lack of appropriate early treatment. Positive result of serum CMV PCR indicates high mortality rate in cancer patients. Pre-emptive antiviral therapy is recommended for better prognosis of these patients.

Acknowledgment

This study was supported by grants from the Tri-Service General Hospital, National Defense Medical Center (TSGH-C99-164).

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