Cytomegalovirus Infection in Non-transplant Patients with Hematologic Neoplasms: A Case Series

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Background: Cytomegalovirus (CMV) infection is uncommon in hematology patients. The clinical pictures and outcomes of this virus are not entirely clear.

Method: Consecutive cases of CMV infection (17 patients with 20 episodes) were compiled for study over a six year period.

Results: CMV infection occurred in patients of various ages and with a number of underlying hematological diseases, including non-Hodgkin's lymphoma, multiple myeloma (MM), acute myeloid leukemia (AML) and myeloproliferative neoplasm, No single laboratory assay was sensitive enough to serve as a screening test in the diagnosis of CMV infection. A combination of laboratory assays, clinical features and radiographic findings were required for diagnosis. All patients with AML or MM had received various chemotherapies before CMV infection. All but one lymphoma patient had received steroids and rituximab treatment prior to CMV infection. CMV infection episodes were accompanied by various co-infections in 60% (12/20) of cases. Bacterial lobar pneumonia was the most common form of co-infection. We used ganciclovir as the sole antiviral treatment in most of the infection episodes (18/20). Anti-CMV immunoglobulin (cytotect) was also provided to one patient because of persistent fever and dyspnea. Treatment was successful in all but one of the cases, which occurred when ganciclovir was initiated after respiratory failure. This patient died of CMV pneumonia. The other patients had good initial responses to antiviral treatment, but their long-term outcome was poor. Only five patients survived after a short follow-up duration.

Conclusions: In an era of intensive immuno-chemotherapy, CMV infection may become a serious threat for hematology patients. Physicians dealing with hematological malignancies should be aware of CMV infection, especially for patients receiving rituximab and steroids.

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Key words: cytomegalovirus, lymphoma, multiple myeloma, leukemia, rituximab

In adult patients, cytomegalovirus (CMV) infection or reactivation usually occurs in immunocompromised hosts, such as patients with acquired immunodeficiency syndrome (AIDS) or organ transplanta-

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tion recipients. For patients with hematological malignancies, CMV infection is infrequent except in stem cell transplant recipients.[1] Other than some scattered case reports, only three case series of CMV infection are available, two describing lymphoma and the other describing leukemia patients.[2-4] All three reports are from the M.D. Anderson Cancer Center. Most of these patients had been seropositive for CMV before clinically overt CMV infection, suggesting that their CMV disease represented reactivation rather than new infection.[4] In Taiwan, the seropositive rate is approximately 50% for school-age children and more than 90% for adults.[5,6] CMV reactivation is a potentially serious threat following treatment of hematologic neoplasms. However, owing to a lack of large serial studies, in-depth knowledge of its clinical manifestations is incomplete and a standard treatment has not been well established. A uniform definition of CMV infection is available.[7] In brief, it can be classified into CMV antigenemia (CMV-A) or CMV disease (CMV-D), depending on the presence of blood CMV antigens or end organ disease. We retrospectively analyzed 17 cases and 20 episodes of CMV infection in patients with hematological neoplasms. In our experience, rituximab and steroids appeared to be associated with CMV infection. Our series suggests that CMV infection indicates a poor prognosis, although the initial treatments appeared to be effective.

METHODS

Patients and treatment

Consecutive cases of CMV infection that were encountered by 3 participating hematologists in the hematology division of Chang Gung Memorial Hospital in Lin-Kou, Taiwan, were collected for this study. The enrollment period was between July 2003 and December 2009. The criteria for enrollment was clinically or pathologically proven CMV infection, including CMV-A and CMV-D, in patients with underlying hematological neoplasms. The types of neoplasms included all types of leukemia, lymphoma, multiple myeloma and chronic myeloproliferative neoplasm (MPN). Treatment for CMV was given at the individual physician's discretion. No uniform guidance for clinical intervention was planned in advance. The clinical features and treatment outcomes were obtained by review of the medical records. The data were analyzed retrospectively.

Detection of CMV infection

In laboratory examinations, the presence of CMV inclusion bodies in the tissue biopsy was interpreted by the pathologists. The histological diagnosis was further confirmed by positive immunohistochemical staining of CMV antigens in tissue sections. Detection of blood CMV pp65 antigens was performed by the immunofluorescence method, as described elsewhere.[2] The result was reported as positive CMV-infected cells per 500,000 polymorphonuclear leukocytes. Serum CMV antibody (IgG and IgM) titers were measured by microparticle enzyme immunoassay. Rapid CMV cultures of urine and bronchoalveolar lavage (BAL) fluid were done by the shell vial method.

The definition of CMV-A and CMV-D has been described by Ljungman et al.[7] In the present study, both CMV-A and CMV-D were included. Coinfection was defined by infection with microorganisms other than CMV within 30 days following diagnosis of CMV infection. Success of CMV treatment was defined as improvement of clinical symptoms and laboratory results (i.e. conversion of CMV pp65 antigenemia to negative). This study was approved by the institutional review board of Chang Gung Memorial Hospital.

RESULTS

The complete clinical and laboratory data of the 17 patients are presented in Table 1. Twenty CMV infection episodes, including 9 CMV-D and 11 CMV-A infections, occurred in 17 patients. Their median age was 61 years (range 29-86). There were 10 men and 7 women. The underlying hematologic neoplasms included non-Hodgkin's lymphoma (NHL) of B-lineage (7 cases, 6 diffuse large B-cell lymphoma, 1 mantle cell lymphoma), acute myeloid leukemia (AML, 5 cases), multiple myeloma (MM, 2 cases), and acute lymphoblastic leukemia (ALL), myeloproliferative neoplasm (essential thrombocythemia in this case) and adult T-cell lymphoma and leukemia (1 case each). All 8 NHL and ATLL patients were men and all 6 AML and ALL patients were women. The true incidence of CMV infection is beyond the scope of this case series but for patients with NHL, a rough estimate is 2.7%. High

Table 1. Complete Clinical and Laboratory Data of Hematologic Patients with CMV Infection

case No	age/ sex	underlying disease	treatment	No of treatment cycles	high dose steroid	CMV type	CMV Ag	Anti-CMV IgG	Anti-CMV IgM	SV (BAL)	SV (urine)	CXR/ HRCT	infection sites	antiviral therapy	duration (days)	coninfection	treatment effect	long term outcome	survival (months)	cause of death
1	29/F	AML	Ara-C based chemotherapy	4	No	CMV-D	(+)	(+)	(–)	ND	(–)	IP/ND	stomach	G	10	NTM (lung)	improved	lost to follow-up	NA	NA
2	51/F	MM	VAD	2	Yes	CMV-D	ND	ND	ND	(+)	(–)	IP/ND	lung	G	14	Bacilli (blood)	improved	expire	12	sepsis
3*	68/F	AML	Ara-C based chemotherapy	7	No	CMV-A	(+)	(+)	(–)	ND	(–)	IP/ND	NA	G	14	No	improved	expire	27	sepsis
4	84/M	MPN	busulfan‡	NA	No	CMV-D	(–)	(+)	(–)	(+)	ND	IP/IP	lung	G	1	A. baumanii (lung)	died	expire	< 1	CMV-D
5	61/F	AML	melphalan‡	NA	No	CMV-D	(–)	(+)	(–)	(+)	ND	IP/ND	lung	G	14	No	improved	expire	6	coinfection
6	84/M	NHL	R-CEOP	13	Yes	CMV-D	ND	ND	ND	ND	ND	IP/ND	stomach	none	none	No	no treatment	expire	< 1	tumor progression
7	58/M	NHL	R-CHOP	1	Yes	CMV-A	(+)	(+)	(–)	ND	ND	CO/ND	NA	G	21	A. baumanii (lung)	improved	expire	< 1	CMV-D
8	45/M	MM	thalidomide and steroid	2	Yes	CMV-A	(+)	(+)	(–)	ND	ND	IP/IP	NA	G	17	No	improved	survive	14	NA
9	86/M	NHL	R-COP	3	Yes	CMV-D	(–)	(+)	(–)	(+)	ND	CO/ND	lung	G	21	S. aureus (lung)	improved	survive	12	NA
10	67/M	NHL	R-COP	2	Yes	CMV-A	(+)	(+)	(–)	(–)	ND	CO/IP	NA	G	12	A. baumanii (lung)	improved	expire	1	coinfection
11	61/M	ATLL	CHOP	1	Yes	CMV-A	(+)	(+)	(–)	ND	ND	IP+CO/ND	NA	G	8	No	improved	expire	5	tumor proression
12*	72/M	NHL	R-COP	3	Yes	CMV-A	(+)	ND	ND	ND	ND	CO/ND	NA	G	18	Mold (lung)	improved	expire	6	coinfection
13	58/F	AML	Ara-C based chemotheraphy	4	No	CMV-A	(+)	ND	ND	ND	ND	IP/IP	NA	G	7	No	improved	survive	6	NA
14*	65/M	NHL	R-COP R-ESHAP	4	Yes	CMV-A	(+)	ND	ND	ND	ND	IP/ND	NA	G	8	S. aureus (lung)	improved	expire	3	tumor progression
15	51/F	AML	Ara-C based chemotheraphy	NA	No	CMV-D	(–)	(+)	(–)	(+)	ND	Normal/ND	lung	G	14	fungus (blood)	unevaluable	survive	6	NA
16	29/M	NHL	R-CHOP ALL	2	Yes	CMV-D	(–)	ND	ND	(+)	ND	IP/IP	lung	G+V	21	influenza (lung)	improved	survive	4	NA
17	37/F	ALL	chemotherapy†	NA	Yes	CMV-D	(+)	(+)	ND	(+)	ND	Normal/ND	lung	G	7	No	improved	expire	11	tumor progression

Abbreviations: AML: acute myeloid leukemia; MM: multiple myeloma; MPN: myeloproliferative neoplasm; VAD: vincristine, adriamycin, dexamethasone; R-CEOP: rituximab, cyclophosphamide, epirubicin, vincristine, prednisolone; R-C(H)OP: rituximab, cyclophosphamide, (adriamycin), vincristine, prednisolone; R-ESHAP: rituximab, etoposide, methylprednisolone, high dose Ara-C, cisplatin; SV-BAL: shell vial culture from bronchoalveolar lavage; CXR: chest radiograph; HRCT: high resolution computed tomography; IP: interstitial pattern; CO: consolidation; ND: Not done; NA: Not applicable; G: ganciclovir; V: valganciclovir; CMV: cytomegalovirus; CMV-A: CMV antigenemia; CMV-D: CMV disease; NHL: Non-Hodgkin's lymphoma; ALL: acute lymphoblastic leukemia; ATLL: adult T-cell lymphomal and leukemia; NTM: non-tuberculous mycobacterium; *: recurrent case of antigenemia; †: multiple combination regimens; ‡: continuous treatment.

dose steroids (defined as a dose of prednisolone 400 mg or higher, or other steroids of equivalent potency, within one month prior to CMV infection) were used in 11 patients, all of whom had NHL, MM or ALL. None of the patients with AML or MPN received steroids. In addition to steroids, all 7 patients with NHL of B-lineage also received rituximab treatment as part of chemotherapy, which in theory contributed to further immune suppression and susceptibility to opportunistic infection. The baseline data of the patients is summarized in Table 2.

Diagnostic yield for CMV detection methods

Seven of the patients with CMV-D had CMV pneumonia, and two had CMV gastritis. In all the cases of CMV pneumonia, the diagnosis was made on the basis of positive shell vial cultures of BAL fluid in addition to clinical symptoms (fever, cough or dyspnea). An immunofluorescence assay to detect pp65 antigens was performed in 6 out of the 7 cases of CMV pneumonia. Five had negative results. The diagnosis of CMV gastritis was made by histology from a stomach tissue biopsy in both cases.

Urine CMV shell vial cultures were done in the first 3 patients. All had negative results. A serology test for CMV antibody of the IgG isotype was done in 11 patients, and all had positive results. A serology test of CMV antibody of the IgM isotype was done in 10 patients. All of them had negative results. The serology test was repeated for 3 patients within 19 to 75 days. Neither seroconversion nor a significant increase in antibody titers was found.

Chest radiographs were available in all CMV infection episodes. In 6 episodes, radiographs revealed patchy or diffuse consolidations. All 6 episodes were confirmed to be accompanied by lobar bacterial pneumonia. In 12 episodes, the radiographs revealed patterns of interstitial pneumonia. The radiographs were normal in 2 cases of CMV-A. High resolution computed tomography (HRCT) scans were done in 6 episodes of CMV infection. Typical interstitial, ground-glass inflammatory reactions were demonstrated in 5 episodes. Diffuse consolidation was found in 1 case, which was also complicated by coinfection with bacterial pneumonia. The laboratory and image findings are summarized in Table 3.

Table 2. Baseline Data before Cytomegalovirus (CMV) Infection

Median age (range)		61 (29-86)
Sex (M/F)		10/7†
Underlying disease		
	B-NHL*	7
	AML	5
	ALL	1
	ATLL	1
	MM	2
	MPN	1
Treatment prior to CMV		
	Ara-C based CT	4
	rituximab-based CT	7
	busulfan	1
	thalidomide and steroids	1
	Other CT‡ (melphalan, VAD, CHOP, Hyper-CVAD)	4
Steroid use§		
	Yes	11

Data reported in number of patients.

Abbreviations: B-NHL: B-lineage Non-Hodgkin's lymphoma; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; ATLL: adult T-cell lymphoma and leukemia; MM: multiple myeloma; MPN: myeloproliferetive neoplasm; CT: chemotherapy; *: 1 mantle cell lymphma and 6 diffuse large B-cell lymphoma; †: All NHL and ATLL patients were men, and all AML and ALL patients were women; ‡: each regimen with one patient; §: defined as prednisolone 400 mg, or equivalent potency, within the prior month.

Efficacy of antiviral treatment

Antiviral treatment was given to 16 patients in 19 episodes. One patient (case 6) did not receive treatment because he had terminal phase lymphoma and poor physical performance status. Ganciclovir was the main antiviral therapy in our series. In one patient (case 16), monotherapy with ganciclovir was insufficient for treatment so cytotect was added. In the other 18 episodes, ganciclovir was the sole initial antiviral therapy. The dose of ganciclovir was adjusted to 100 mg three times weekly according to renal function in case 10. In the remaining episodes, ganciclovir 250 to 500 mg per day was administered for 1 to 21 days. In the 19 episodes managed with ganciclovir treatment, 17 had improved CMV infection. One patient (case 4) died one day after initiating antiviral treatment.

Coinfection and outcomes

Coinfection occurred in 12 out of 20 episodes in our series. In 4 patients, the coinfection was the direct cause of or contributed to the patient's death. In particular, 3 of the 4 patients surviving for less than a month had coinfections. These results suggest that coinfection has an important and debilitating impact on the short-term prognosis of hematologic patients with CMV infection.

The long-term outcomes of patients with hematologic neoplasms and CMV infection was poor in our series. Four out of 17 patients died within one month of documented CMV infection. Six patients died subsequently within 5 to 27 months. Only 5 patients survived to the time of writing this article. The follow-up time for these patients was relatively short (4 to 14 months). The treatment and outcomes of patients are presented in Table 4.

DISCUSSION

Trend of increasing CMV infection

CMV infection usually occurs in immunocompromised hosts such as recipients of organ transplants, patients with AIDS or those taking immunosuppressives.[8] CMV infection may occur in patients with hematological malignancies. The majority of cases are stem cell transplant recipients or patients with chronic lymphocytic leukemia, especially after treatment with alemtuzumab.[9,10] Other than in the transplant milieu, CMV infection is uncommon for patients with hematologic neoplasms. In large-scale

Table 3. Laboratory and Radiographic Results of Infection Episodes

CMV infection type		
	CMV-D	9/20
	CMV-A	11/20
CMV antigen		
	Positive	13/18
	negative	5/18
CMV IgG		
	Positive	11/11
CMV IgM		
	Positive	0/10
shell vial (BAL)		
	Positive	7/7
shell vial (urine)		
	Positive	0/3
radiograph		
	interstitial	12/20
	consolidation	6/20
	normal	2/20
CT scan		
	interstitial	5/6
	consolidation	1/6

Data reported in number of infection episodes (event number/episode number).

Table 4. Treatment Results, Coinfections and Outcomes

Antiviral therapy		
	ganciclovir	18/20
	ganciclovir+cytotect	1/20
	None	1/20
Treatment duration		
	median 14 days	(1-21 days)
Treatment success		17/19
	Coinfection	12/20
	lobar pneumonia	7
	sepsis	1
	invasive fungus infection	2
	NTM	1
	Influenza	1
Outcome		
	died	10
	survived	5*
	lost to follow-up	1
Cause of death		
	CMV disease	2
	bacterial infection	4
	tumor progression	4

Abbreviations: NTM: non-tuberculous mycobaterium; *: follow-up 4-14 months.

Data reported in number of infection episodes (event number/episode number)

autopsy reports, CMV infection was found in 0.2-0.3% of cancer patients.[11] The incidence was 0.4% for patients with leukemia.[12] Although the incidence is low, there is a trend of increasing incidence of CMV infection over time in clinical reports of both lymphoma and leukemia.[3,4] The higher incidence may result from increasing awareness of CMV infection and more serious immunosuppression caused by the increased treatment intensity of immunochemotherapies. For both reasons, it is likely that CMV infection will continue to rise and thus become an important clinical problem among patients with hematological malignancies.

Our cases were collected over a span of 6 years. With a small sample size, we could not identify any trend of increasing incidence over time. However, 9 out of the latest 11 episodes of CMV infection occurred in patients with lymphoma. The estimated incidence of 2.7% was higher than in previous reports from western countries. The following factors may account for this incidence: (1) The high prevalence of pre-existing CMV infection in Taiwan.[5,6] (2) More severe immunosuppression caused by new target therapies and immunotherapies, such as rituximab. (3) The increased awareness of CMV infection and therefore, increased rates of diagnosis, among such patients. Except for one patient with ATLL, all patients received rituximab and steroids in addition to chemotherapy. Because rituximab and steroids are becoming commonplace in the treatment of B-cell lymphoma, we speculate that CMV reactivation will become an important clinical issue in areas with high CMV seropositive rates, such as Taiwan.

Features of patients with CMV infection

Our patient data showed CMV infection occurred over a broad range of ages (from 29 to 86 years, median 61 years) and with a wide variety of underlying diseases (AML, ALL, NHL, MM and MPN). The gender distribution of our patients is interesting. All 6 patients with acute leukemia were women and all 8 patients with lymphoma were men. A male predominant distribution of lymphoma patients with CMV infection was also found in another study. Chemaly et al. reported 36 episodes of CMV pneumonia among lymphoma patients. Twenty-seven episodes occurred in men and 9 in women.[3] Likewise, Torres reported 71 patients with 82 episodes of CMV infection among lymphoma patients, and 62% of CMV infected patients were men. This gender difference of CMV infection risk has also been observed among immunocompetent hosts and patients undergoing liver transplantation.[13,14] It is so far unclear why the incidence of CMV infection differs between sexes. Further large-scale studies are needed to confirm this novel observation and investigate its etiology.

Possible risk factors of CMV infection

We did not identify any unique risk factor of CMV infection for patients with AML, ALL or MPN. All patients with lymphoma or myeloma had received steroid treatment prior to CMV infection. In addition, 7 out of 8 lymphoma patients received rituximab as part of combination chemotherapy. Rituximab has been associated with various opportunistic infections because of its profound immunosuppression.[15,16] Although we did not have a control group for comparison, our data revealed a relationship between the use of rituximab/steroids and the development of CMV infection. Similar to our observations, Aksoy et al. reported recently that lymphoma patients treated with rituximab had virus reactivation, the most common of which were hepatitis virus B (39.1%) and CMV (23.4%).[17] Close monitoring of hepatitis B and CMV was suggested in lymphoma patients treated with rituximab-based regimens.[17] Further cohort or case control studies are needed to validate rituximab or steroids as risk factors for CMV infection.

Association of CMV and busulfan

To the best of our knowledge, there is no report of MPN patients developing CMV infection in the literature. Case 4 in our study was relatively elderly and had been given busulfan before CMV infection. Busulfan can be used as a cytoreductive therapy for MPN.[18] As part of the conditioning chemotherapy before stem cell transplantation, high dose busulfan is associated with severe immunosuppression, thus rendering patients at risk of opportunistic infections, including CMV.[19] For treatment of MPN, there is no direct evidence showing the daily low dose of busulfan will cause sufficient immunosuppression for the development of opportunistic infections. However, there are scattered reports of chronic myeloid leukemia patients who developed non-tuberculous mycobacterial (NTM) infection after busulfan treat-

ment.[20] Taken together, it is possible that patients who take busulfan for this purpose are nevertheless susceptible to opportunistic infections, such as NTM in previous reports and CMV in our study.

Radiographic features of CMV infection

Although CMV may infect various target organs, the predominant sites of clinically significant infection are the lungs and blood.[3,4,11,12] Although only 7 patients were documented with CMV pneumonia in our series, abnormal image findings shown by chest radiographs could be found in 90% (18/20) of infection episodes. Interstitial infiltration was the main abnormality found (12/20). Patchy consolidation was shown in 6 cases, all of which were later found with superimposed bacterial pneumonia. HRCT, as in our series, may provide further confirmative evidence, but it is not absolutely necessary in the diagnosis of CMV infection.

Laboratory assays in detection of CMV infection

The unequivocal diagnosis of CMV infection can be made by histology findings. However, obtaining tissue biopsies is an invasive procedure and alternative diagnostic measures are often necessary.

Clinically, the diagnosis of CMV infection is made by positive virus cultures in sterile sites or by typical serology results (positive CMV IgM or 3-fold rise of CMV IgG).[21] In our series, the serology test did not have any diagnostic value. CMV IgG was positive but IgM was negative in all cases with available serology data. No patient had significantly increased titers of CMV IgG. The measurement of pp65 antigens had positive results in 72% (13/18) of infection episodes, including one patient with CMV pneumonia and one with CMV gastritis. However, CMV antigenemia was not sensitive for patients with confirmed CMV pneumonia. Only 1 of the 7 cases with positive shell vial CMV cultures was positive for blood CMV antigens. Urine CMV cultures were done in the first 3 patients. None of them had positive results. Taken together, no single assay in the current report had sufficient sensitivity to serve as a screening test for CMV infection in patients with hematologic neoplasms. The diagnosis of CMV infection relies on a combination of various laboratory diagnostic measures. For patients with suspected CMV pneumonia, absence of CMV antigenemia should not exclude the diagnosis and a BAL fluid shell vial culture should be done.

Treatment efficacy and outcomes of patients with CMV infection

The outcomes of CMV infected patients with hematologic malignancies were poor in previous reports. For leukemia patients, the CMV pneumonia–associated mortality rate was 57%. Six months after pneumonia, the mortality increased to 82%.[4] For lymphoma patients, the mortality directly attributable to CMV pneumonia was 30%.[3] In the present study, there were 5 survivors and the longest follow-up duration was 14 months. However, in the present study, most death did not result directly from CMV infection. In the 10 cases whose causes of death were evaluable, only 2 died of CMV- related etiologies. The rest of the patients died either from subsequent infection or cancer progression. Judging from our limited data, these patients had either profound immunosuppression or refractory malignancies, which led to inferior overall outcomes. Despite the poor outcomes, antiviral treatment was highly effective. In the 19 episodes with ganciclovir treatment, 17 had improvement of CMV infection. We needed to add cytotect in one case because of CMV infection that was possibly resistant to ganciclovir. This initial success possibly illustrates the importance of early initiation of antiviral therapies, as the only overt failure occurred in a patient who received ganciclovir after respiratory failure. The importance of early intervention was also supported in other studies. In the report of Nguyen et al., CMV infection led to an overall mortality of 57% in leukemia patients. If the antiviral treatment was initiated after respiratory failure, the mortality was 100%.

Coinfection occurs frequently among hematology patients with CMV infection. Chemaly et al. reported a coinfection rate of 53% for lymphoma patients with 31% of patients already having coinfection upon diagnosis of CMV pneumonia.[3] The occurrence of coinfection in the present study was close to that in the report by Chemaly et al. Twelve out of 20 patients (60%) had various coinfections, including bacteremia, NTM pneumonia and other bacterial pneumonia. Not all coinfection contributed to patient mortality. However, when providing supportive care, it is important for clinicians to keep in mind that coinfection must be considered even for

patients with confirmed CMV infection.

The standard treatment of CMV infection in patients with hematological malignancies is yet to be established. In the present study, only ganciclovir in various doses was given at the choice of the physician. The treatment duration ranged from 8 to 21 days. Except for a patient with uremia, the minimum dose of ganciclovir was 250 mg per day. All dosing schedules appeared to be effective in our series. We hope this experience can be the foundation of future large-scale studies and the optimal treatment dosing schedule and maintenance for CMV infection can be established.

Conclusions

CMV infection occurs at various ages and with various underlying hematologic diseases, including lymphoma, myeloma, AML, ALL and MPN. Patients using steroids and rituximab are particularly at risk. The gender difference in CMV infection rates is marked and requires further investigation. There is frequent coinfection for CMV-infected patients. Antiviral therapies are effective when started early but most patients succumb to advanced cancer or subsequent infection due to compromised immunity. In the era of intensive immuno-chemotherapy, CMV infection will likely become a clinically important issue and clinicians treating hematologic neoplasms should be aware of this potentially life-threatening complication in order to initiate timely and proper treatment.

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REFERENCES

1. Ljungman P, Reusser P, de la CR, Einsele H, Engelhard D, Ribaud P, Ward K. Management of CMV infections: recommendations from the infectious diseases working party of the EBMT. Bone Marrow Transplant 2004;33:1075-81.
2. Torres HA, Kontoyiannis DP, Aguilera EA, Younes A, Luna MA, Tarrand JJ, Nogueras GM, Raad II, Chemaly RF. Cytomegalovirus infection in patients with lymphoma: an important cause of morbidity and mortality. Clin Lymphoma Myeloma 2006;6:393-8.
3. Chemaly RF, Torres HA, Hachem RY, Nogueras GM, Aguilera EA, Younes A, Luna MA, Rodriguez G, Tarrand JJ, Raad II. Cytomegalovirus pneumonia in patients with lymphoma. Cancer 2005;104:1213-20.
4. Nguyen Q, Estey E, Raad I, Rolston K, Kantarjian H, Jacobson K, Konoplev S, Ghosh S, Luna M, Tarrand J, Whimbey E. Cytomegalovirus pneumonia in adults with leukemia: an emerging problem. Clin Infect Dis 2001;32:539-45.
5. Shen CY, Chang WW, Chang SF, Chao MF, Huang ES, Wu CW. Seroepidemiology of cytomegalovirus infection among children between the ages of 4 and 12 years in Taiwan. J Med Virol 1992;37:72-5.
6. Chen MH, Chen PC, Jeng SF, Hsieh CJ, Su FC, Liao HF, Su YN, Lin SJ, Hsieh WS. High perinatal seroprevalence of cytomegalovirus in northern Taiwan. J Paediatr Child Health 2008;44:166-9.
7. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 2002;34:1094-7.
8. Tnani N, Massoumi A, Lortholary O, Soussan P, Prinseau J, Baglin A, Hanslik T. Management of cytomegalovirus infections in patients treated with immunosuppressive drugs for chronic inflammatory diseases. Rev Med Interne 2008;29:305-10.
9. Osterborg A, Foa R, Bezares RF, Dearden C, Dyer MJ, Geisler C, Lin TS, Montillo M, van Oers MH, Wendtner CM, Rai KR. Management guidelines for the use of alemtuzumab in chronic lymphocytic leukemia. Leukemia 2009;23:1980-8
10. Nguyen DD, Cao TM, Dugan K, Starcher SA, Fechter RL, Coutre SE. Cytomegalovirus viremia during Campath-1H therapy for relapsed and refractory chronic lymphocytic leukemia and prolymphocytic leukemia. Clin Lymphoma 2002;3:105-10.
11. Rosen P, Hajdu S. Cytomegalovirus inclusion disease at autopsy of patients with cancer. Am J Clin Pathol 1971;55:749-56.
12. Mera JR, Whimbey E, Elting L, Preti A, Luna MA, Bruner JM, Williams T, Bodey GP, Goodrich JM. Cytomegalovirus pneumonia in adult nontransplantation patients with cancer: review of 20 cases occurring from 1964 through 1990. Clin Infect Dis 1996;22:1046-50.
13. Razonable RR. Cytomegalovirus infection after liver transplantation: current concepts and challenges. World J Gastroenterol 2008;14:4849-60.
14. Galiatsatos P, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. Dig Dis Sci 2005;50:609-16.
15. Chang H, Yeh HC, Su YC, Lee MH. Pneumocystis jiroveci pneumonia in patients with non-Hodgkin's lymphoma receiving chemotherapy containing rituximab. J Chin Med Assoc 2008;71:579-82.
16. Aksoy S, Dizdar O, Hayran M, Harputluoglu H. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic

review and meta-analysis. Leuk Lymphoma 2009;50:357-65.
17. Aksoy S, Harputluoglu H, Kilickap S, Dede DS, Dizdar O, Altundag K, Barista I. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 2007;48:1307-12.
18. Palandri F, Catani L, Testoni N, Ottaviani E, Polverelli N, Fiacchini M, De Vivo A, Salmi F, Lucchesi A, Baccarani M, Vianelli N. Long-term follow-up of 386 consecutive patients with essential thrombocythemia: safety of cytoreductive therapy. Am J Hematol 2009;84:215-20.
19. Schetelig J, Oswald O, Steuer N, Radonic A, Thulke S, Held TK, Oertel J, Nitsche A, Siegert W. Cytomegalovirus infections in allogeneic stem cell recipients after reduced-intensity or myeloablative conditioning assessed by quantitative PCR and pp65-antigenemia. Bone Marrow Transplant 2003;32:695-701.
20. Watanabe K, Sueishi K, Tanaka K, Nagata N, Hirose N, Shigematsu N, Miake S, Yoshida M. Pulmonary alveolar proteinosis and disseminated atypical mycobacteriosis in a patient with busulfan lung. Acta Pathol Jpn 1990;40:63-6.
21. The CARI guidelines. CMV disease and kidney transplant: diagnostic tests for cytomegalovirus in renal transplantation. Nephrology 2004;9 Suppl 3:S23-6.

非移植血液惡性病患的巨細胞病毒感染

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背 景： 巨細胞病毒 (Cytomegalovirus, CMV) 感染在血液疾病之病患並不常見。學界對其臨床特徵及疾病全貌尚未完全清楚。

方 法： 我們在 6 年期間連續性地蒐集了 17 位巨細胞病毒感染的血液惡性疾病患者，一共 20 次的感染以資研究。

結 果： 巨細胞病毒感染發生在各種年齡與不同的背景疾病，包含非何杰金氏淋巴瘤、多發性骨髓瘤、急性白血病及慢性骨髓增生症。在診斷方面，沒有任何單一的實驗診斷方式具有足夠的敏感度可以作爲篩檢巨大細胞病毒的工具，必須綜合臨床表徵、實驗及影像學診斷、才能確定診斷。在危險因子方面，所有急性白血病及多發性骨髓瘤患者都在感染之前曾接受化學治療，淋巴瘤病患除一人之外都曾接受類固醇及莫須瘤 (rituximab) 的治療。此外，百分之六十的病患合併有其他感染，其中以細菌性肺炎最爲常見。治療上多數病患接受 ganciclovir 單一治療，一位病患因持續性症狀而須加上 cytotect 治療。除了一位病患外，巨細胞病毒的治療皆告成功，唯一失敗案例可能是因爲病患較晚 (在發生呼吸衰竭後) 才開始接受抗病毒治療。雖然初始治療效果甚佳，這些病患的整體預後並不理想，至發稿爲止，僅 5 位病患仍然存活。

結 論： 隨著血液惡性疾病治療強度的增加，巨細胞病毒感染可能成爲血液疾病，尤其是接受類固醇及莫須瘤的患者的嚴重威脅，醫師應提高警覺以及時作出正確有效的處理。

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關鍵詞： 巨細胞病毒，淋巴瘤，多發性骨髓瘤，白血病，莫須瘤

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