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Cytomegalovirus Surveillance and Prevention in Allogeneic Bone Marrow Transplantation: Examination of a Preemptive Plan of Ganciclovir Therapy

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Forty-two cytomegalovirus (CMV)-seropositive allogeneic marrow transplant patients or recipients of CMV-seropositive marrow allografts were entered into a surveillance program to detect and treat CMV infection during the first 120 days posttransplant. CMV infection was detected at a mean time of day 50 in 21/37 (58%) patients who had surveillance cultures. Twelve of 42 (28%) received preemptive ganciclovir treatment for virus isolated from blood (9 patients) or from bronchoalveolar lavage fluid (3 patients), and all had no CMV-associated sequelae. CMV disease was diagnosed in 5 patients (4 with pneumonia, 1 with gastroenteritis) who did not have positive cultures until the onset of their disease. CMV-related mortality was 4/42 (10%). Patients who earlier manifested lung injury or diffuse alveolar hemorrhage (DAH) were significantly predisposed to subsequent CMV pneumonia ($P = 0.0013$, Fisher's exact test) at a median onset of day 42. Restricted prophylactic use of ganciclovir in such patients may be indicated. Fifty percent of all patients never required ganciclovir during the surveillance period. When compared to a universal prophylaxis program of ganciclovir for the prevention of CMV disease, the use of ganciclovir in a preemptive strategy could avoid unnecessary therapy for a substantial number of patients and earn significant cost-savings. © 1996 Wiley-Liss, Inc.

Key words: cytomegalovirus, ganciclovir, bone marrow transplant, pneumonia, allogeneic

INTRODUCTION

Cytomegalovirus (CMV) pneumonia is a major cause of death following allogeneic marrow transplantation [1]. Combination therapy with ganciclovir and intravenous immunoglobulin has reportedly decreased mortality due to CMV pneumonia from 85% to 50% [2–4]. However, the effectiveness of therapy is clearly related to early diagnosis before patients develop symptoms requiring mechanical ventilation [3]. Moreover, despite advances in therapy, patients recovering from CMV pneumonia have a 6-month survival of only 30–40% because of frequent infections with other opportunistic pathogens such as gram-negative bacteria and fungi [4,5].

Recent strategies have focused on the prevention of CMV infection long before the development of symptomatic disease [6,7]. In the CMV-seronegative patient with a CMV-seronegative marrow donor, the use of CMV-seronegative blood products has virtually eliminated primary CMV infection [8–11]. Intravenous immunoglobulin (IVIG) has been used to decrease the incidence of acute graft-vs.-host-disease as well as the occurrence of interstitial pneumonia, despite its unclear role in reducing the incidence of CMV infection itself [12–15].

CMV-seropositive patients and CMV-seronegative recipients of CMV-seropositive marrow allografts are *at-risk* for reactivation of CMV and subsequent disease. Universal prophylaxis with ganciclovir for all CMV at-risk patients has been shown to reduce the incidence of CMV infection and pneumonia in uncontrolled [16,17] and randomized controlled [18,19] studies. However, this prophylactic approach may be very expensive and sub-

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TABLE I. Patient Characteristics

No. of patients	42
Median age in years (range)	31 (7–58)
Sex (male/female)	28/14
Underlying diagnoses	
Chronic myeloid leukemia	16
Acute myeloid leukemia	8
Acute lymphoid leukemia	5
Chronic lymphocytic leukemia	3
Lymphoma	4
Aplastic anemia	3
Myelodysplasia	2
Metabolic disorder	1
Donor type	
Related, matched	25
Related, mismatched	3
Unrelated, matched	9
Unrelated, mismatched	5
CMV status pretransplant	
Recipient+/Donor±	37
Recipient−/Donor+	5
Preparative regimen	
Chemotherapy alone	21
Chemotherapy + irradiation	21

jects many patients unnecessarily to a myelotoxic agent. An alternative strategy of early treatment with ganciclovir for positive surveillance cultures is also effective in reducing the incidence of CMV disease in treated patients vs. controls [20,21]. Data from these studies indicate that positive CMV cultures obtained from bronchoalveolar lavage (BAL) fluid on day 35 or from blood have a predictive value of 60–70% for the development of CMV pneumonia [20–22].

At our institution, we surveyed CMV at-risk patients for CMV infection by cultures of BAL fluid taken around day 35 and by weekly samples from blood, throat, and urine. Preemptive treatment with ganciclovir was initiated for positive CMV cultures from BAL fluid or from blood. This study describes the utility and results of this approach in reducing CMV-related mortality during the first 120 days after allogeneic transplant.

PATIENTS AND METHODS

Patient Characteristics

CMV at-risk patients included all allogeneic transplant recipients with positive pretransplant serology for CMV or who had CMV-seropositive bone marrow donors. The characteristics of 42 consecutive CMV at-risk patients from October 1991–March 1994 are summarized in Table I.

Transplant Protocol

All allogeneic transplants were performed in a high-efficiency, particulate-filtered environment. Graft-vs.-host disease prophylaxis consisted of short-course methotrexate and cyclosporine A. Donor marrow was given without T cell depletion. IVIG at 500 mg/kg/dose was given to all patients weekly beginning at the time of preparative regimen through the first 3 months posttransplant, then once a month for a year. Acyclovir at 5 mg/kg every 8 hr intravenously was given to patients with positive herpes simplex titers. Ciprofloxacin and fluconazole were part of the antimicrobial prophylactic regimen. For *Pneumocystis carinii* prophylaxis, trimethoprimsulfamethoxazole was given on admission until day −1 and resumed twice a week after adequate hematologic recovery.

All cellular blood products were irradiated (2,500 cGy), and their leukocyte content was reduced by filtration. CMV-negative blood products were routinely given to CMV-seronegative recipients. CMV-seropositive recipients received unscreened blood products.

Initial treatment for graft-vs.-host disease consisted of methylprednisolone at 2 mg/kg/day for 14 days with subsequent tapering. Antithymocyte globulin was added for steroid failures, including those with a lack of response or progression within 1 week of full-dose steroids or a flare of at least grade II graft-vs.-host disease while still on a relatively high dose of steroids.

Patients underwent weekly chest roentgenographs. Diagnostic bronchoscopy was performed for patients who were found to have pulmonary infiltrates. The bronchoalveolar lavage fluid was routinely examined and cultured for microbiologic pathogens including *Pneumocystis carinii, Mycoplasma pneumoniae, Legionella* sp., *Mycobacteria,* fungi, viruses such as CMV, and herpes simplex. Some patients presented abruptly with respiratory distress with or without hemoptysis, and with diffuse pulmonary infiltrates around the period of neutrophil recovery (day 10–20) usually preceded by high-grade fever not responding to empiric antibiotics or antifungal therapy. On bronchoalveolar lavage studies, no identifiable pathogens were found, but the alveolar fluid became bloodier on repeated lavages. This form of early lung injury has been described elsewhere in autologous bone marrow transplant recipients as diffuse alveolar hemorrhage (DAH) [23], and has been included at our center as a diagnosis applicable in the allogeneic transplant patient as well.

CMV Surveillance Program

Beginning October 1991, each CMV at-risk patient was entered into a program of CMV surveillance cultures from BAL fluid obtained between day 33–42. Weekly cultures of CMV from blood, throat, and urine samples were also obtained. For the first 27 patients, weekly isolations began around day 35. The subsequent 15 patients had isolations started as early as day 20. All routine surveillance cultures continued until day 120.

Both rapid centrifugation and conventional cultures were performed on all samples. Results from rapid centrif-

ugation cultures were obtainable the next day. Conventional cultures were carried for 5 weeks if rapid centrifugation culture results were negative.

Preemptive therapy for CMV, defined as treatment for asymptomatic infection to prevent progression to disease, was started for positive cultures from the BAL sample or from blood. For patients who had persistent asymptomatic CMV excretion in the urine (>1 week), a repeat BAL for CMV was performed. Prophylactic therapy for CMV, defined as treatment given to high-risk patients before onset of CMV infection, was initiated beginning day 28 for the last 3 patients who recovered from diffuse alveolar hemorrhage.

For preemptive and for prophylactic therapy, ganciclovir was given at 5 mg/kg intravenously twice daily for 14 days of induction and continued at 5 mg/kg/day intravenously, 5 days/week (Monday–Friday) until day 120. CMV disease (pneumonia, gastroenteritis) was treated with an induction course of ganciclovir at 5 mg/kg intravenously twice daily for 21 days, and IVIG 500 mg/kg every other day for 10 doses. This was followed with at least 4 weeks of maintenance ganciclovir at 5 mg/kg/day for 5 days/week (Monday–Friday) or until day 120, whichever resulted in the longer course. Granulocytopenia occurring during ganciclovir use was managed initially by dose reduction or discontinuation of the drug. As recombinant growth factors became available, filgrastim was employed when granulocyte counts decreased to $<2.5 \times 10^9$/l to allow full dose administration of ganciclovir.

Statistical Analysis

Chi-square analysis was performed to evaluate patient characteristics that may be associated with CMV pneumonia, and results were confirmed by Fisher's exact test where appropriate. The Mann-Whitney rank sum test was used to evaluate the difference in blood product requirements between patients receiving ganciclovir or not.

TABLE II. CMV Surveillance Findings

Early deaths (non-CMV-related)			5
Patients with surveillance cultures			37
Patients with previous DAH		9	
CMV pneumonia	3		
CMV viremia	3		
Prophylactic ganciclovir	3		
Patients with no DAH		28	
CMV pneumonia	1		
CMV gastroenteritis	1		
CMV viremia	7		
BAL fluid+	3		
CMV viruria	3		
No CMV excretion	13		
Total			42

TABLE III. Chi-Square Analyses of Variables Related to CMV Pneumonia and DAH*

	Proportion with CMV pneumonia[a]		Proportion with DAH
Variable	(N = 22)	(N = 37)	(N = 42)
Graft-vs.-host disease			
Yes	3/17	4/24	6/24
No	0/5	0/13	3/18
P	0.788	0.315	0.786
Donor			
Unrelated	2/6	3/13	6/14
Related	1/16	1/24	3/28
P	0.476	0.311	0.138
Regimen			
+TBI	2/9	3/17	7/21
−TBI	1/13	1/20	2/21
P	0.823	0.563	0.250
DAH			
Yes	3/3	3/9	
No	0/19	1/28	
P	0.010	0.124	

*DAH, diffuse alveolar hemorrhage; TBI, total body irradiation.
[a]Analyses for first 27 (N = 22) and all 42 (N = 37) patients, excluding five early deaths.

RESULTS

Five of 42 patients suffered, within 35 days posttransplant, complications leading to early death from causes not associated with CMV: two with sepsis, two with venoocclusive disease of the liver, and one with aspergillosis. The remaining 37 patients had at least one surveillance culture for CMV initiated (Table II).

Diffuse Alveolar Hemorrhage and CMV

Patients who developed very early (<day 30) BAL culture-negative pulmonary infiltrates with hemorrhagic BAL fluid returns were considered to have diffuse alveolar hemorrhage (DAH) [23]. Nine of 42 (21%) patients were diagnosed with DAH. High-dose methylprednisolone (1,000 mg/day) [24] administered on a rapidly tapering schedule was very effective in the resolution of pulmonary infiltrates and improvement of symptoms in these patients. The first three patients who earlier in their transplant course had DAH subsequently acquired new pulmonary infiltrates positive for CMV on days 40, 42, and 47. All three died after failing therapy with the combination of ganciclovir and IVIG. Cultures for CMV prior to diagnosis of pneumonia in all 3 patients were negative.

Because of the development of CMV pneumonia in 3 cases who had previous lung injury, an interim analysis for the first 27 patients was performed (Table III). The presence of graft-vs.-host disease, the donor source, or the use of total body irradiation in the preparative regimen did not have prognostic significance for an association with CMV pneumonia. However, there was a statistically

significant correlation of CMV pneumonia and a previous diagnosis of DAH ($P = 0.01$, chi-square test; $P = 0.0013$, Fisher's exact test). Thus, our management policy for patients who developed DAH was modified: prophylactic ganciclovir was initiated on day 28, a time when most patients would have had adequate marrow engraftment, and 2 weeks before the onset of pneumonia. Earlier surveillance for CMV was also initiated before day 28 in DAH patients. Of the next 6 patients who were treated for DAH, CMV viremia was diagnosed in 3 before day 28 (day 20, day 21, and day 25). All 6 received ganciclovir treatment by day 28. None developed CMV disease. Two of the 6 are alive after >9 months posttransplant despite the fact that one of them had persistent viremia during maintenance ganciclovir. Four patients died of various non-CMV-related causes before day 120: 1 with severe refractory graft-vs.-host disease (GVHD) (day 47), 1 with intracranial bleed (day 53), 1 with disseminated aspergillosis (day 67), and 1 with septic shock syndrome (day 97).

Subsequent analysis that included all 42 patients showed the loss of statistical significance for an association between CMV pneumonia and DAH (Table III). This loss of statistical significance was attributable to the change in policy of selective early treatment with ganciclovir for the last 6 DAH patients resulting in the prevention of CMV disease in this group. Certain patient characteristics were also evaluated for correlation with development of DAH. DAH was frequently seen in patients with severe graft-vs.-host disease (50% vs. 15%), in unrelated transplants (43% vs. 11%), and in those who received total body irradiation (33% vs. 10%), but these differences did not reach statistical significance (Table III).

Patients Without DAH

Of 28 patients who did not have DAH and survived past day 35, one acquired CMV pneumonia after becoming severely debilitated from a hemorrhagic stroke. All CMV surveillance cultures before diagnosis of pneumonia, including a BAL sample from day 35, were negative in this patient. Another had a pulmonary infiltrate on day 34, and a BAL on day 35 negative for CMV, and died of disseminated aspergillosis on day 53. The remaining 26 patients were asymptomatic when BAL was done between day 33–42. Only 2 were positive for CMV. Of the 24 who were initially BAL-negative, subsequent follow-up showed 6 with viremia, 5 with viruria, and 1 with biopsy-proven CMV gastroenteritis. The patient with gastroenteritis also had a positive blood culture only at the onset of CMV disease. She fully recovered after treatment with ganciclovir and IVIG, and is alive 9+ months out.

Of the 5 viruria cases, 2 had nonpersistent excretion (only one urine sample positive for CMV). The other 3 with persistent positive CMV cultures in urine underwent repeat BAL: 1 was positive at day 68; the other 2 were negative (day 60, day 69), but 1 later became viremic at day 112. None of the 5 patients in this group developed CMV disease.

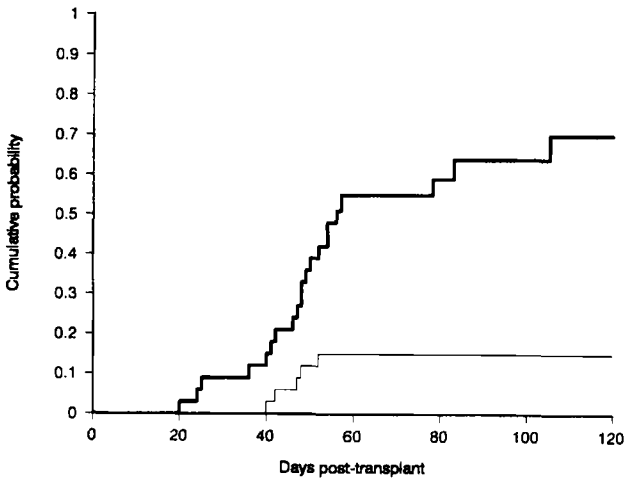

Fig. 1. Kaplan-Meier product limit estimate of probability of acquiring CMV infection (thick line) or disease (thin line) during first 120 days posttransplant.

Thirteen of 37 (35%) patients who had surveillance cultures never had any evidence of CMV reactivation up to day 120. However, 1 developed CMV pneumonia on day 171 outside the surveillance period, but recovered completely after appropriate therapy with ganciclovir and IVIG.

CMV Incidence and Mortality

Twenty-one patients developed CMV infection during the first 120 days posttransplant. Figure 1 plots out the probability of acquiring CMV infection for the entire group: at the end of 120 days, the cumulative incidence is 0.70. The median time to reactivation of CMV is day 48 (range, days 20–105). Five patients had CMV disease with onset at a median time of day 47 (range, days 40–54): 4 with pneumonia, and 1 with gastroenteritis. The cumulative probability of acquiring CMV disease is 0.15 (Fig. 1). Pneumonia accounted for the CMV-related mortality of 4/42 (10%). None were prospectively detected by surveillance cultures before onset of disease, precluding early preemptive therapy with ganciclovir. As described earlier, 3 patients who died of CMV pneumonia had a previous diagnosis of DAH. The 120-day overall survival for the entire group is 0.65 (Fig. 2).

Use of Ganciclovir

Preemptive therapy was given for any patient who had viremia or positive BAL. Twelve patients received preemptive treatment (3 for +BAL, and 9 for viremia): 2 died of other causes (aspergillosis on day 67, severe graft-vs.-host disease on day 47), and the other 10 developed no CMV-related sequelae (Table IV).

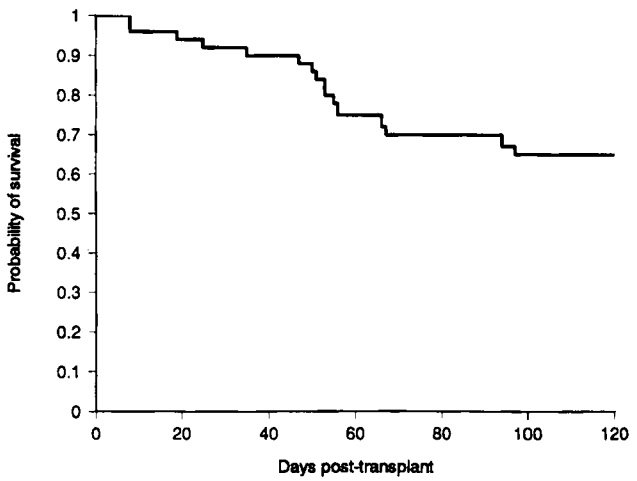

Fig. 2. Kaplan-Meier product limit estimate of probability of overall survival up to day 120 posttransplant.

TABLE IV. Frequency of Ganciclovir Use

Indication for use	Number	%
Prophylactic	3	7
Preemptive	12	28
Therapeutic	4	10
Indicated but not given[a]	2	5
None	21	50
Total	42	100

[a]One patient was severely debilitated from a hemorrhagic stroke; another had rapid septic death before therapy could be started.

Development of significant ganciclovir-related granulocytopenia was obviated by the use of granulocyte colony-stimulating factor (filgrastim) 1–5 times a week if total white count declined to $<2.5 \times 10^9$/l, to allow full dose administration of ganciclovir until day 120. Patients receiving ganciclovir significantly required more red cell transfusions than those who did not receive ganciclovir (mean number of units ± SD: 29 ± 15 vs. 22 ± 18, $P = 0.039$). Platelet transfusions also tended to be more frequent in ganciclovir recipients though not reaching significance (mean number of single-donor platelet units ± SD: 36 ± 24 vs. 24 ± 19, $P = 0.076$).

Overall, during the surveillance period, 21/42 (50%) did not require ganciclovir.

Projected Comparative Cost Analysis

We analyzed the projected cost of our preemptive program vs. that of a previously published prophylactic strategy of CMV prevention in allogeneic transplant recipients [18]. Calculations were made based on an 80-kg standard patient using doses of the prophylactic ganciclovir schedule from Winston et al. [18] and our own ganciclovir dosing schedule for preemptive treatment, including costs for therapeutic ganciclovir in about 10% of patients in each group as well as costs for surveillance testing. The projected savings are substantial, on the order of 44% in favor of preemptive strategy (Table V). These projected calculations exclude the additional costs of blood product support or growth factors that are magnified with extensive use of ganciclovir.

DISCUSSION

Cytomegalovirus is a major cause of morbidity and mortality in CMV at-risk allogeneic transplant recipients. The realization that early treatment to prevent life-threatening CMV pneumonia significantly reduces CMV-related mortality has led to the use of various strategies aimed at decreasing the chances of acquiring the disease [7]. However, there is no consensus standard approach in achieving this end. Many transplant centers in Europe perform surveillance cultures or other diagnostic tests to detect CMV, and treat preemptively with ganciclovir at time of positive detection [25]. A few others give ganciclovir to patients who are CMV-seropositive up front during the risk period (first 80–120 days) of acquiring CMV infection posttransplant. In the U.S., four randomized trials (two using the preemptive treatment approach and two using the prophylactic approach) have shown that ganciclovir given early can reduce the incidence of CMV pneumonia or disease in treated patients [18–21].

We have described the results of our strategy of CMV surveillance mainly relying on a preemptive approach to treat BAL+ or viremic patients. Both BAL positivity and viremia have been shown to have a predictive value of 60–70% for the development of CMV pneumonia [4,22,26]. None of our patients treated in this manner developed any CMV-related sequelae. Unfortunately, as also seen by other investigators, some patients in this study presented with positive cultures only at the time when they developed disease or symptoms, thus negating a preemptive line of therapy. Treatment at this time with ganciclovir plus IVIG may not be very effective. Four cases (10%) of all our CMV at-risk patients developed CMV pneumonia, and subsequently died of their disease despite treatment with ganciclovir and IVIG in 3 of these cases. The use of more sensitive detection methods, such as the CMV antigenemia assay or polymerase chain reaction (PCR) for CMV DNA, may be better surveillance tools than isolation of CMV by culture [27–29]. Various reports have indicated 1–2 weeks lead time of detection by these methods compared to current culture techniques [29]. Indeed, some centers are using CMV antigenemia alone in place of culture methods in their surveillance programs [25]. Preliminary data employing the antigenemia assay by Boeckh et al. [30] showed that all patients with CMV pneumonia had positive antigenemia detected

TABLE V. Projected Cost Analysis of CMV Prevention Plans Using Ganciclovir*

	Preemptive plan		Prophylactic plan	
Indication	Percentage	Dollar cost	Percentage	Dollar cost
Prophylactic ganciclovir	7	73,695.00	100	1,275,750.00
Preemptive ganciclovir	33	280,593.00	0	0.00
Therapeutic ganciclovir	10	299,042.00	10	284,462.00
Not requiring ganciclovir	50	0.00	0	0.00
Surveillance tests		368,000.00		261,300.00
Total		1,021,330.00		1,821,512.00
Potential savings		800,182.00 (44%)		

*Assumptions: 100 patients per group; dose of ganciclovir based on 80 kg standard per person. Prophylactic plan adapted from Winston et al. [18], where ganciclovir was given 2.5 mg/kg every 8 hr × 1 week pretransplant, and then resumed at 6 mg/kg/day Monday–Friday every week for approximately 14 weeks posttransplant. Therapeutic ganciclovir included cost of IVIG 500 mg/kg every other day × 10 doses; cost of 3 weeks' worth of ganciclovir prophylaxis deducted from therapeutic ganciclovir cost under Prophylactic plan. Prophylactic ganciclovir cost under Preemptive plan is based on treatment started on day 28, while preemptive ganciclovir cost is based on mean treatment starting time of day 50. Cost of performing bronchoalveolar lavage added to surveillance tests cost under Preemptive plan. See Patients and Methods for dosing schedule of ganciclovir used under Preemptive plan.

earlier, even though they had negative surveillance cultures before onset of pneumonia.

Rather than giving ganciclovir universally to all CMV at-risk patients up front, we identified a subgroup of patients most likely to reactivate CMV or to develop fatal CMV pneumonia and who, therefore, may benefit from a more selective prophylactic use of ganciclovir. The first 3 patients who had early lung injury in the form of DAH and who were treated with high doses of steroids all succumbed to CMV pneumonia. Pulmonary infiltrates in DAH usually develop prior to 30 days posttransplant, and in our experience respond remarkably well to high-dose methylprednisolone that is rapidly tapered. Most patients will have complete resolution of their infiltrates and may or may not require transient ventilatory support. All 3 patients subsequently developed new infiltrates between day 40–47 that were positive for CMV by BAL. One had concomitant viremia when pneumonia was diagnosed. The pulmonary injury associated with DAH seems to predispose lung tissue to CMV infection. The use of high doses of steroids at the same time allows a situation for the greatest risk of CMV reactivation. Indeed, when routine surveillance cultures for CMV were obtained earlier (beginning as early as day 20) in the subsequent 6 patients who had DAH, 3 had documented viremia on days 20, 21, and 25, respectively. Ganciclovir was initiated in all 6 patients beginning day 28. Although 4 of these 6 patients died before day 120, none died from CMV-related causes. Two are alive >9 months after transplantation.

The terminology of DAH has been primarily reported in the autologous transplant literature [23,24,31]. In the allogeneic transplant setting, references have been made to idiopathic interstitial pneumonitis or idiopathic pneumonia syndrome in patients who develop pulmonary infiltrates that are negative for known microbiologic pathogens. Reports from various centers suggest that interstitial pneumonitis is associated with cytomegalovirus infections in 30–70% of cases [32]. Up to 60% of cases are referred to as idiopathic and more likely represent undiagnosed infections, drug or radiation toxicity, or possible immune reactions involving the lung [32]. Our analysis of factors associated with the diagnosis of DAH has shown a greater incidence in patients with severe graft-vs.-host disease, in unrelated transplants, or in patients who receive total body irradiation, but the small patient numbers do not allow a difference reaching statistical significance. Treatment for idiopathic interstitial pneumonitis has not been addressed clearly in the literature. It has a case fatality rate of 78%, similar to the reported mortality rate of 80% for untreated DAH [23]. Since the description by Chao et al. [24] of effective treatment of DAH syndrome in autologous transplant patients using high-dose methylprednisolone, we have extended this form of treatment to our allogeneic transplant patients who have diffuse pulmonary infiltrates and meet criteria for DAH diagnosis: BAL washings that successively become bloodier, in the absence of a microbiologic pathogen. The incidence of DAH in our study is 21%, similar to that reported in the autologous transplant situation.

The mechanism underlying the increased incidence of CMV pneumonia in DAH patients is not clear. CMV is an intracellular organism that can replicate in the leukocyte [33,34]. Patients who develop DAH have a high number of neutrophils (bronchial neutrophilia) in their bronchial lavage fluid during their pretransplant BAL examination [31]. The time of occurrence of DAH corresponds to the period when patients are starting to engraft [23] and neutrophil counts start to rise (day 10–20). Neutrophils and other leukocytes (eosinophils) may be implicated in

initiating or amplifying lung injury in DAH, as exemplified in human and animal models of adult respiratory distress syndrome (ARDS) [31]. The resulting inflammatory reaction in bronchial and lung tissue attracts leukocytes that may be latently infected with CMV. Virologic culture of BAL fluid specimens in DAH patients at this time does not reveal CMV. It is not known whether PCR for CMV genome may detect latent CMV in the lavage fluid of DAH patients. High-dose steroids may modify the natural history of DAH by attenuating neutrophil function, but on the other hand could cause further immunosuppression of cytotoxic T cell function, including that specific against CMV. Other factors, such as immunologic attack from graft-vs.-host disease and radiation-associated effects on lung tissue, may contribute to host injury that predisposes to development of CMV pneumonia.

Although ganciclovir is very active against CMV, it is far from being an ideal agent for a CMV prevention plan. Clinically significant neutropenia requiring dose modification or cessation of therapy has been observed in 30–58% of cases [18,19,21]. In one particular study, patients who became neutropenic from ganciclovir prophylaxis had an associated increased risk for bacterial infection during the period of neutropenia [19]. When ganciclovir is started early at time of engraftment, the neutropenic toxicity could last an average of 12 days after discontinuing the drug [19]. We have tried to use recombinant growth factors in our patients receiving ganciclovir before granulocyte counts drop significantly ($<2.5 \times 10^9$/l), rather than stopping therapy or adjusting the dose. Requirements for packed red cells and platelets have been increased in our patients, as has been observed by others [17,18]. Ganciclovir prophylaxis may also contribute to a delay in the recovery of CMV-specific T cell responses that are required for complete protection from CMV disease. This effect has been implicated in the development of 2 cases of CMV pneumonia after day 100 in patients who had received ganciclovir prophylaxis and had not recovered protective CD8+ CMV-specific cytotoxic response [35]. The aim of a preemptive strategy is to be able to avoid unnecessary therapy for a substantial number of patients, which in our study represents half the total, who would otherwise be universally put on a prophylactic program. The use of prophylactic ganciclovir could be restricted to the subgroup of patients at highest risk for CMV pneumonia, which in our institution would include those who develop DAH.

More effort and time are certainly involved in any preemptive strategy. Until such time as a less toxic but at least equally effective alternative agent is available for treatment of CMV, vigilant surveillance and preemptive treatment programs combined with a risk-adapted strategy of selective prophylaxis offer a feasible, more cost-effective CMV prevention plan, as compared to universal prophylaxis.

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