EARLY TREATMENT WITH GANCICLOVIR TO PREVENT CYTOMEGALOVIRUS DISEASE AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

JAMES M. GOODRICH, PH.D., M.D., MOTOMI MORI, PH.D., CURT A. GLEAVES, M.S., CHARLES DU MOND, PH.D., MONICA CAYS, R.N., DARLENE F. EBELING, M.S., WILLIAM C. BUHLES, PH.D., BERNADETTE DEARMOND, M.D., M.P.H., AND JOEL D. MEYERS, M.D.*

Abstract *Background.* Cytomegalovirus (CMV) infection is a major cause of morbidity and mortality after allogeneic bone marrow transplantation. We conducted a controlled trial of ganciclovir for the early treatment of CMV infection in asymptomatic recipients of bone marrow transplants whose surveillance cultures for CMV became positive.

Methods. Bone marrow–allograft recipients who were seropositive for CMV antibodies or who received seropositive marrow were screened for CMV excretion by culture of throat swabs, blood, urine, or bronchoalveolar-lavage fluid. In this double-blind trial, 72 patients who had marrow engraftment and were excreting virus were randomly assigned to receive either placebo or ganciclovir (5 mg per kilogram of body weight twice a day for one week, followed by 5 mg per kilogram per day) for the first 100 days after transplantation. Patients were followed for the development of biopsy-confirmed CMV disease, ganciclovir-related toxicity, and survival.

Results. Between assignment to the study drug and day 100 after transplantation, CMV disease developed in only 1 of the 37 patients assigned to receive ganciclovir (3 percent), but in 15 of the 35 patients assigned to receive placebo (43 percent, $P<0.00001$). The ganciclovir recipients had rapid suppression of virus excretion; 85 percent had negative cultures after one week of treatment, as compared with 44 percent of the placebo group ($P = 0.001$). The principal toxic reaction was neutropenia; 11 ganciclovir recipients had an absolute neutrophil count below 0.75×10^9 per liter, as compared with 3 placebo recipients ($P = 0.052$). Treatment was discontinued in 11 ganciclovir recipients and 1 placebo recipient because of neutropenia ($P = 0.003$). After treatment was stopped, the neutrophil count recovered in all patients. Overall survival was significantly greater in the ganciclovir group than in the placebo group both 100 days and 180 days after transplantation ($P = 0.041$ and 0.027, respectively).

Conclusions. Early treatment with ganciclovir in patients with positive surveillance cultures reduces the incidence of CMV disease and improves survival after allogeneic bone marrow transplantation. (N Engl J Med 1991;325:1601-7.)

Characteristics of the Study Groups.

Table 1. Characteristics of the Study Groups.

CHARACTERISTIC	GANCICLOVIR	PLACEBO
No. of patients	37	35
Age — mean yr (range)	33 (3–56)	31 (3–51)
Sex — M/F	20/17	15/20
Underlying disease — no. (%)		
Acute lymphocytic leukemia	5 (14)	7 (20)
Acute nonlymphocytic leukemia	16 (43)	11 (31)
Chronic myelogenous leukemia	11 (30)	11 (31)
Hodgkin's disease	1 (3)	0
Non-Hodgkin's lymphoma	2 (5)	4 (11)
Other	2 (5)	2 (6)
HLA matching — no. (%)		
Patient matched with related donor	21 (57)	27 (77)
Patient matched with unrelated donor	5 (14)	6 (17)
Patient mismatched with donor	11 (30)*	2 (6)
Acute GVHD — no. (%)		
Present	25 (68)	24 (69)
Not present	12 (32)	11 (31)
CMV status before transplantation — no. (%)		
Patient negative, donor positive	6 (16)	3 (9)
Patient positive, donor negative	12 (32)	14 (40)
Patient and donor positive	19 (51)	18 (51)
Days from transplantation to study entry — mean (range)	54 (18–79)	48 (16–77)
Administration of immune globulin — no. (%)†	12 (32)	7 (20)

*P = 0.03 for the comparison with the number of patients with mismatching in the placebo group.

†Five ganciclovir recipients and four placebo recipients received 500 mg of immune globulin per kilogram per week as part of a protocol for the prevention of acute GVHD. The other 10 patients received immune globulin on an irregular basis to supplement low serum immunoglobulin levels.

Goodrich JM et al. N Engl J Med 1991;325:1601-1607.

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Occurrence of CMV Disease.

Table 2. Occurrence of CMV Disease.

Occurrence of CMV	Ganciclovir (N = 37)	Placebo (N = 35)	P Value
Between start of study drug and day 100			
Probability of CMV disease — % (SE)*	3.0 (3.0)	53 (10)	<0.00001†
No. with CMV disease	1	15	—
Type of disease — no.			
Pneumonia	1	10‡	—
Gastrointestinal	0	6‡	—
Between start of study drug and day 180			
Incidence of CMV disease — %	16	43	0.013§
No. with CMV disease	6	15	—
Type of disease — no.			
Pneumonia	2	10¶	—
Gastrointestinal	3‖	7¶	—
Retinitis	1‖	0	—
Lingual infection	1	0	—

*Kaplan–Meier product-limit estimate of probability (and standard error of the mean) during the first 100 days after transplantation or until termination of the study, if earlier.

†By log-rank test.

‡One patient had both pneumonia and gastrointestinal disease.

§By Cochran–Mantel–Haenszel chi-square test stratified according to the presence or absence of GVHD at study entry.

¶One patient had both pneumonia and gastrointestinal disease before day 100 and a recurrence of gastrointestinal disease on day 125.

‖One patient had both retinitis and gastrointestinal disease.

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Detection of Excretion of CMV.

Table 3. Detection of Excretion of CMV.

Time of Detection	Patients with Cultures	Patients Positive (%)*	P Value†
Study entry			
Ganciclovir	37	37 (100)	
Placebo	35	35 (100)	
Day 2–4			
Ganciclovir	28	10 (36)	0.57
Placebo	25	11 (44)	
Day 7			
Ganciclovir	33	5 (15)	0.001
Placebo	32	18 (56)	
Week 2			
Ganciclovir	31	2 (6)	0.001
Placebo	28	19 (68)	
Week 3			
Ganciclovir	30	0	0.001
Placebo	26	16 (62)	
Week 4			
Ganciclovir	24	0	0.001
Placebo	20	16 (80)	
Week 5			
Ganciclovir	21	0	0.001
Placebo	14	11 (79)	
Week 6			
Ganciclovir	14	0	0.003
Placebo	9	5 (56)	
Week 7			
Ganciclovir	9	0	0.003
Placebo	11	6 (55)	
End of study			
Ganciclovir	6	0	0.018
Placebo	6	4 (67)	

*A patient was considered to have a positive culture if any culture from any specimen was positive during the period shown.

†By Cochran–Mantel–Haenszel chi-square test comparing the treatment groups for the proportion of patients with positive CMV cultures, with stratification for the presence or absence of GVHD at study entry.

Goodrich JM et al. N Engl J Med 1991;325:1601-1607.

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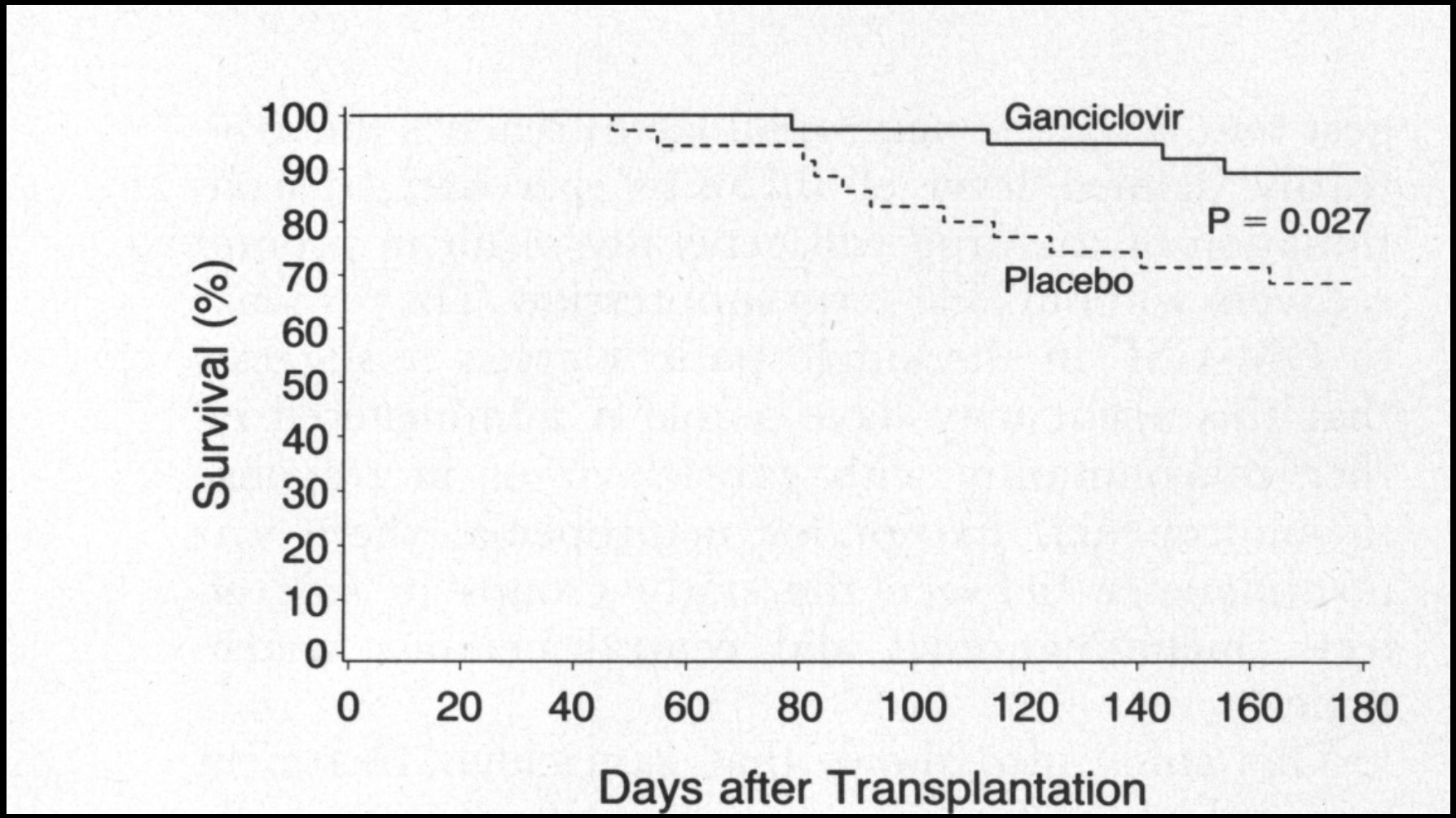
Kaplan–Meier Product-Limit Estimates of the Probability of Survival during the First 180 Days after Transplantation among Ganciclovir and Placebo Recipients.



Goodrich JM et al. N Engl J Med 1991;325:1601-1607.

Effect of Ganciclovir Treatment on the Absolute Neutrophil Count.*

Table 4. Effect of Ganciclovir Treatment on the Absolute Neutrophil Count.*

Count	Ganciclovir (N = 37)	Placebo (N = 35)	P Value
	no. of patients		
$<1.0\times10^9$/liter	15	7	0.12†
$<0.75\times10^9$/liter	11	3	0.052†
$<0.5\times10^9$/liter	6	1	0.11†
Neutropenia requiring cessation of treatment	11	1	0.003‡

*The patients represented had absolute neutrophil counts that decreased below the level indicated for two or more consecutive days either during treatment or within two days after its discontinuation.

†By log-rank test.

‡By two-tailed Fisher's exact test.

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Analyses

Weekly viral load

Extended CMV disease and mortality analyses

Correlation of viral load with clinical enpoints