

## Cytomegalovirus infection in orthotopic liver transplantation

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**Abstract.** We retrospectively studied 175 orthotopic liver transplants in 151 patients. Of the 151 patients, 59 (39.1%) were diagnosed as having cytomegalovirus (CMV) infection. The rate of infection in patients treated for rejection was 48.8% as compared to 26.2% in patients without rejection ( $P < 0.01$ ). Antirejection therapy was associated with culture-positive cases in 33 out of 43 patients as compared to 9 out of 16 patients who had CMV antibody titer elevations. Patients were treated with gancyclovir if they had simultaneous positive cultures from multiple sites and were seriously ill. Eighteen of the 19 patients thus treated had side effects, one of which was serious (bone marrow hypoplasia). Cultures became negative in 15 out of 17 (88%) of the surviving patients. Patient survival was similar to our overall survival rate of 87%.

**Key words:** Liver transplantation, and cytomegalovirus infection - Cytomegalovirus infection, in liver transplantation - Gancyclovir, for cytomegalovirus infection, in liver transplantation.

Cytomegalovirus (CMV) infection is a well-recognized complication of solid organ transplantation procedures. Between December 1984 and December 1987, the incidence of CMV pneumonia in liver and kidney transplant patients at Baylor University Medical Center was 7.7% and 2.8%, respectively [12]. The incidence of symptomatic CMV infection in liver transplant patients at the University of Pittsburgh was reportedly 22.0% [10]. CMV infection is reported to be the most frequent complication of liver transplantation procedures at the Mayo Clinic [9].

Recently gancyclovir, 9-[1,3 dihydroxy-2-proxymethyl] guanine (DHPG), an analogue of acyclovir, has emerged as an effective antiviral agent capable of inhibiting CMV replication and of benefiting patients with severe CMV infection [3, 4, 7, 8,

13, 20, 21]. In studies carried out *in vitro*, gancyclovir has been demonstrated to inhibit CMV replication in cell cultures [4, 13, 20, 21]. Ultrastructural studies revealed that gancyclovir inhibited the formation of viral cores and the production of nucleocapsids, enveloped virions, and dense bodies. However, it did not prevent the formation of virus-induced intranuclear tubular structures [4]. Gancyclovir was also found to be effective in reducing CMV shedding in solid organ transplant recipients and was well tolerated. Relapses were infrequent in these patients in contrast to patients with the acquired immunodeficiency syndrome (AIDS) [3, 7].

In liver transplant patients, treatment options for CMV with reduced immunosuppression alone are limited because of the possibility of increased incidence of life-threatening graft rejection. This could lead to graft loss and patient death as experienced at the University of Pittsburgh Medical Center, where all five patients with CMV pneumonia died [10].

In this report we present our experience with CMV infections in liver transplant patients. We place special emphasis on those patients treated with gancyclovir for severe culture-proven CMV disease.

### Materials and methods

Between December 1984 and April 1988, 175 orthotopic liver transplants (OLT) were performed in 151 patients. The age of the patients ranged from 4 to 65 years with a mean of 41.9 years. There were 68 males and 83 females. Donors were selected on the basis of body size and ABO compatibility. Only three ABO-mismatched, compatible transplants were performed. Immunosuppression was based on cyclosporin (CyA) and prednisolone (P). Patients with good preoperative renal function [glomerular filtration rate (GFR) greater than 40 ml/min] received 10 mg/kg CyA orally or 2 mg/kg IV along with 50 mg P orally or IV preoperatively. During surgery a single dose of 1000 mg hydrocortisone was given. If the patient was diuresing, CyA was given at a dose of 1-2 mg/kg IV every 12 h. Prior to November 1986, attempts were made to maintain CyA levels at 800-1200 ng/ml (whole blood RIA); administration was oral or IV, depending on how it was best tolerated. Since November 1986, CyA levels of 600-800 ng/ml have been the goal. In patients with poor renal function preoperatively (hepatorenal syndrome or GFR less than 40 ml/min), no CyA is given preoperatively; instead, patients re-

ceive 3 mg/kg azathioprine (AZA) IV. CyA is withheld or used at greatly decreased levels and AZA is continued until renal function recovers.

Prior to November 1986, only 19.7% of all patients were started on AZA perioperatively as compared to 50% since that time. Patients received a tapering dose of P (from 200 mg to 20 mg/day over 6 days) postoperatively. Rejection was diagnosed clinically and histologically and treated with a single dose of 1000 mg methylprednisolone, followed by a P recycle. Rejections resistant to this were treated with OKT3 therapy. The duration of OKT3 therapy ranged from 10 to 26 days with a mean of 13.7 days.

Patients were followed up with daily lab investigations, and weekly bacterial, fungal, and viral surveillance of body fluids was performed. Secretions from nose and throat were examined, as were specimens of sputum and urine. Serological determination of CMV, Epstein-Barr virus, herpes simplex virus I and II, and varicella zoster virus IgM and IgG antibodies were done on a weekly basis. Weekly liver graft biopsies were obtained for pathological examination, and viral culture and liver biopsies were also obtained for suspected rejection. Biopsies and cultures from other sites, such as the gastrointestinal tract and lung, were done if necessary, according to the clinical presentation of the patients. The viral cultures were performed using standard cell culture tube methodology with rhesus monkey kidney A-549 and MRC-5 cell lines. In addition, since late 1985, early detection has been achieved using MRC-5 shell viral centrifugation enhancement with CMV early nuclear monoclonal antibody labelling for detection within 36-72 h [5, 6, 15, 19, 20]. Buffy coat cultures were done using the above-mentioned techniques after recovering WBCs from a heparinized blood specimen using mono-poly resolving medium. Viral titers for CMV were done by applying the indirect fluorescent antibody technique.

The diagnosis of CMV infection was based on the following criteria: (a) a fourfold increase in antibody titer (positive IgM titer  $\geq 10$  and positive IgG titer  $\geq 40$ ), (b) biopsies containing CMV inclusion bodies or positive for CMV early nuclear antigen by direct immunofluorescence, (c) positive viral cultures from any site (except isolated urine cultures), or (d) a combination of any of the above.

Prior to the introduction of gancyclovir in our center in June of 1986, standard care for transplant recipients with CMV infection was based on the reduction of immunosuppression to booster immune defense and on the empiric use of antibiotics to treat secondary infection. After its introduction, gancyclovir was given to patients with severe systemic disease. This included symptomatic patients (those with fever, arthralgia, generalized fatigue) who had a serological response to the infection and had developed CMV in multiple sites simultaneously. In patients with a GFR greater than 30 ml/min, the dosage was 10 mg/kg per day administered IV. In patients with a GFR greater than 10 ml/min but less than 30 ml/min, the dosage was 5 mg/kg per day. When the GFR was less than 10 ml/min, the dosage was 2.5 mg/kg per day.

Gancyclovir was administered IV in normal saline for 1 h. It was given for 10-14 days, depending on clinical response. Some patients with severe CMV disease were treated with commercially available gamma globulin (Gamimune N; Miles-Cutter Biological Elkhart, IN, USA), in addition to the gancyclovir therapy.

## Results

### Incidence

Fifty-nine of 151 patients (39.1%) were diagnosed by the above-mentioned criteria as having CMV infection. The rate of infection in primary transplants was

**Table 1.** Average number of units of blood products used in transfusions

	CMV-infected patients (n=59)	Patients with no CMV infection (n=92)
Intraoperative RBC	8.3	10.8
Postoperative RBC	8.8	7.3
Intraoperative platelets	11.7	14.2
Postoperative platelets	13.6	11.9
Intraoperative FFP	11.5	12.8
Postoperative FFP	7.9	9.9
Intraoperative cryo	12.8	17.4
Postoperative cryo	5.6	6.1

RBC, red blood cells; FFP, fresh frozen plasma; cryo, cryoprecipitate

41.0% (52/127) and in retransplants 29.3% (7/24). Based on antibody titers, the incidences of primary CMV infection and reactivation were 32.2% (19/59) and 67.8% (40/59), respectively. There was a predominance of primary CMV infection among culture-positive cases (12/19) as compared to cases with high titers only (7/19). The age and sex distribution of CMV-infected patients did not differ from that of the entire group, except for the predominance of females in the younger age groups. There was no predisposition to CMV infection according to the liver disease necessitating transplantation. Onset was usually during the 3rd week post-transplant (mean 35.6 days, mode 25 days) but occurred as early as the 2nd postoperative day in retransplants (mean 19 days). There was no significant difference between the kind or the mean number of units of intraoperative and postoperative blood products transfused into the infected patients and into patients who did not develop CMV infection (Table 1).

Patients were classified into two groups. Group 1 consisted of 40 patients who were not treated with gancyclovir. Some of these patients had developed CMV disease before and others after the drug was introduced in our center. The diagnostic criteria for these patients ranged from isolated high CMV antibody titers with negative cultures and no symptoms (16/40) to positive CMV cultures with or without a significant rise in titers (24/40). In spite of the fact that 26 of the 40 patients were infected after gancyclovir had been introduced, reduced immunosuppression was the only treatment given. Four patients in this group were symptomatic and had isolated positive liver biopsy cultures.

Group 2 consisted of 19 patients who were treated with gancyclovir. These patients had simultaneous positive cultures from multiple sites and were symptomatic and seriously ill.

Therefore, the incidence of culture-positive disease was 28.5% (43/151) and that of symptomatic

CMV disease 15.2% (23/151). Figure 1 indicates the different infection sites in all culture-positive patients. It shows a predominance of isolated hepatic disease (21/43), which is nearly as common as cases with extrahepatic disease (respiratory tract: 8/43; other sites: 5/43) plus hepatic and extrahepatic disease (liver and respiratory tract: 9/43) combined. As can be seen, pulmonary involvement stands out among the extrahepatic cases.

#### Relation of CMV infection to rejection and antirejection treatment

All but two infected patients were on triple immunosuppression therapy; the two who were not both had positive CMV cultures. Previous rejection was very common in patients developing CMV infection. In culture-proven cases, the mean onset of infection after treatment for rejection was 22 days. Overall, 86 of the 151 patients (58.9%) experienced rejection. Of these, 42 (48.8%) developed CMV infection after the onset of antirejection treatment, as compared to only 17 out of 65 (26.2%) cases of CMV infection in patients not developing rejection ( $P < 0.01$  by chi-square analysis). The incidence of two rejection episodes in the study population was 15.7%. Of the 42 patients who developed rejection and CMV infection, 17 had two rejection episodes (40.5%). The other 25 patients had one rejection episode only.

#### CMV infection and OKT3 antirejection treatment

Of the 48 patients who received OKT3 therapy, 23 patients (47.9%) developed CMV infection, as compared to 25 patients (52.1%) who did not. This was not statistically significant by chi-square analysis. Of 42 patients with both rejection and CMV infection, 23 (54.8%) received OKT3 and 19 (45.2%) did not. This was also not statistically significant.

#### Gancyclovir-treated patients

Table 2 lists the clinical characteristics of the patients treated with gancyclovir according to the guidelines described earlier. All of these patients had positive cultures from more than one site simultaneously indicating severe infection. They also had multiple concomitant (mainly bacterial) infections indicative of severe immunosuppression. Fifteen of the 19 patients received concurrent antibiotic therapy. Modalities of treatment in these 19 patients included gancyclovir alone ( $n=3$ ), gancyclovir and polyclonal gamma globulin ( $n=9$ ), gancyclovir along with reduction of immunosuppression ( $n=2$ ), and all three

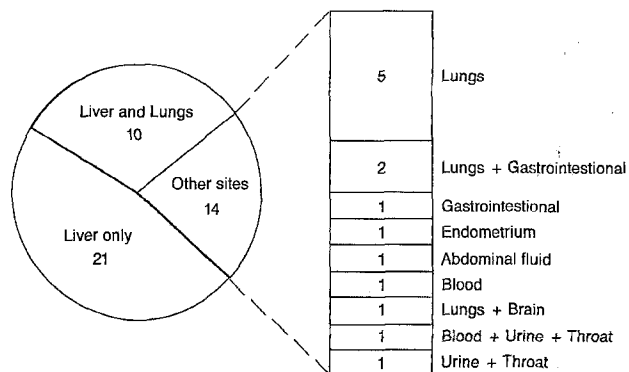


Fig. 1. Sites of positive culture in CMV-infected liver recipients. (Numbers refer to infectious episodes, not to patients)

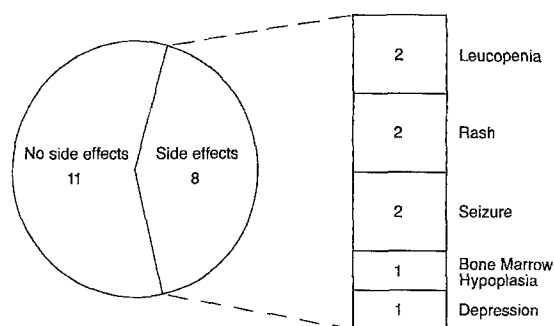


Fig. 2. Side effects of gancyclovir treatment in CMV-infected culture-proven liver transplant patients

modalities combined ( $n=5$ ). Thus, 14 of the 19 patients received gamma globulin.

#### Side effects of gancyclovir therapy

Figure 2 shows the different side effects of gancyclovir that occurred in eight patients. They include leukopenia ( $n=2$ ), rash ( $n=2$ ), seizure ( $n=2$ ), bone marrow hypoplasia ( $n=1$ ), and mental depression ( $n=1$ ). The group of patients who experienced these side effects included six patients who were receiving concurrent antibiotic therapy with such drugs as ampicillin, aminoglycosides, vancomycin, rifampin, cephalosporins, amphotericin B, timentin, and bactrim. Tegretol was also given to some of these patients along with gancyclovir treatment. Two of the eight patients who had side effects were being treated with gancyclovir alone at the time the side effects occurred. One developed a rash and the other had a seizure.

#### Outcome

Blood and other cultures eventually became negative in 16 of the 19 patients treated (84.2%), as can be seen in Table 3. Only one patient had a relapse of the

**Table 2.** Clinical characteristics of gancyclovir-treated patients. Rej, Rejection; Tx, transplantation; Rx, therapy; GIT, gastrointestinal tract; HSV, herpes simplex virus; OLTX, orthotopic liver transplantation; m, month; y, year

Patient number	Num-ber of Tx	Rej	OKT3	Dura-tion	Gammi-mune	Days onset Tx/Days onset Rej	Type of syndrome	Length of Rx (days)	Concomitant problems	Ultimate outcome
1	1	+	+	12	+	18/11	Hepatitis	14	-	Alive & well (6m > OLTX)
2	1	+	-	-	+	32/23	Hepatitis/ pneumonia	14	<i>Pneumocystis</i> pneumonia	Alive & well (7m > OLTX)
3	1	-	-	-	+	25/-	Hepatitis/ pneumonia	12	<i>Pneumocystis</i> pneumonia, pseudomembranous colitis, pancreatitis, bile leak (-repaired)	Alive & well (7.5m > OLTX)
4a	1	+	-	-	+	34/23	GIT (esophagus, duodenum)	12	HSV infection	Alive & well (8m > OLTX)
4b					+		GIT, pneumonia	14	-	
5	1	+	+	10	+	26/18	Hepatitis/ pneumonia	14	-	Alive & well (1y3m > OLTX)
6	2	+	-	-	+	2/-9 <sup>a</sup>	Pneumonia	14	HSV infection	Died after Rx (disseminated CMV infection + <i>Pseudo-</i> <i>monas Serratia</i> sepsis)
7	1	+	+	14	+	50/36	GIT pneumonia (intubated)	22	-	Alive & well (1y5m > OLTX)
8	1	+	-	-	-	28/21	Hepatitis	10	-	Alive & well (1y1m > OLTX)
9	1	-	-	-	-	42/-	Hepatitis	12	-	Alive & well (1y1m > OLTX)
10	1	+	-	-	+	25/18	Pneumonia/ encephalitis	4	Fever, acute pancreatitis, abscess formation	Died (septic shock & respi- ratory failure)
11	2	-	-	-	-	8/-	Hepatitis/ pneumonia	7	-	Alive & well (1.5y > OLTX)
12	3	-	+	8	-	24/-	Hepatitis/ pneumonia	11	-	Alive & well (1.5y > OLTX)
13	1	+	+	12	+	17/23	Hepatitis	11	-	Alive & well (1.5y > OLTX)
14	1	-	-	-	+	41/-	Hepatitis GIT (duodenum)	14	-	Alive & well (4m > OLTX)
15	1	+	-	-	-	19/ 6	Pneumonia	14	-	Alive & well (6m > OLTX)
16	1	+	-	-	+	49/39	Hepatitis	14	-	Alive & well (5m > OLTX)
17	2	+	+	12	+	30/23	Hepatitis/ pneumonia	14	-	Alive & well (11m > OLTX)
18	2	-	-	-	+	31/-	Hepatitis	12	-	Alive & well (1y > OLTX)
19	1	+	+	12	+	28/22	Hepatitis	14	-	Alive & well (3m > OLTX)

<sup>a</sup> Infection occurred 9 days before onset of antirejection therapy

infection and was treated with a second course of gancyclovir 5 days after completion of the first course. There was subsequent clinical improvement and his cultures cleared.

Thirty-three of the 40 patients (82.5%) not treated with gancyclovir survived. The causes of death in this group included adult respiratory distress syndrome (ARDS) with anoxic brain damage, cardiopulmonary dysfunction, sepsis, respiratory and renal failure, and graft failure (patient not a candidate for retransplant).

Seventeen of the 19 gancyclovir-treated patients (89.5%) survived. Causes of death included sepsis from a pancreatic abscess in one patient and generalized sepsis and respiratory failure in the other. CMV was detected in the lungs of both patients at autopsy.

These survival rates are comparable to our overall survival rate of 87.0%.

## Discussion

CMV infection is reported to be one of the most common infections following solid organ transplant procedures. Its importance stems from the fact that it is common and that it is associated with serious morbidity and mortality in a significant number of cases. It can affect every organ system and must be searched for vigorously. It may be found presenting symptoms in unusual locations. For example, unexplained lower abdominal pain in two of our female liver transplant patients necessitated screening for CMV infection, and CMV endometritis was documented in these patients. Fortunately, severe symptomatic CMV disease can now be treated using the new antiviral agent, gancyclovir, as experienced and reported in many transplant centers [3, 7, 8].

Total incidence of CMV infection in liver transplant patients at our center was 39.1%. This is com-

**Table 3.** Positive culture results from patients treated with gancyclovir (DHPG) from December 1984 to April 1988. U, Urine; T, throat; LBX, liver biopsy; BCC, buffy coat culture; Br, bronchial; Bx, biopsy

Pat. No.	Before DHPG therapy	During DHPG therapy	After DHPG therapy
1	U, T, LBX, BCC	U, LBX	None
2	Lung Bx, Br wash	U, LBX	None
3	U, BCC	Br brush, Br wash, LBX	U, Duodenum Bx
4a	U, T, Duodenum Bx	U, T, BCC	U, T, Duodenum Bx, Ulcer Bx, Esophagus Bx, Br brush, Br wash, BCC
4b	U, T, Duodenum Bx, Ulcer Bx, Esophagus Bx, Br brush, Br wash, BCC	None	None
5	U, Br wash, Br brush	U	None
6	Br brush	None	None
7	U, T, Jejunum Bx	Br brush, Br wash, Sputum, U, T, BCC	None
8	U, T	None reported	Ascitic fluid (eventually negative)
9	U, LBX, BCC	None	None
10	Br wash	None	Lung Bx
11	U, Br wash, Br brush	Sputum, T, LBX	U, Sputum (eventually negative)
12	Br wash, Br brush	Pleural fluid, Br wash, Br brush	Lung Bx, Br brush, Br wash, T, Sputum (eventually negative)
13	U	None	None
14	None	LBX	Duodenum Bx
15	BCC, Br wash	None	None
16	LBX	BCC	None
17	U, LBX	Br wash, Br brush	None
18	U, BCC, LBX, Br wash, Br brush		None
19	U, BCC	LBX	None

parable to incidences reported at other centers, such as Pittsburgh, UCLA, and the Mayo Clinic. The incidence of severe symptomatic culture-positive CMV disease was 15.2%, comparable to the 22.0% incidence reported from Pittsburgh [10]. Before the introduction of gancyclovir in our center, 41 patients had already undergone OLTX. The incidence of CMV infection in these patients was 34.1% (14/41). Five of these 14 patients had positive CMV cultures (35.7%). After the introduction of gancyclovir, the incidence was 41.0% (45/110). Thirty-nine of the 45 patients (86.7%) had positive CMV cultures. This increase in the number of culture-positive patients may be attributed to the employment of new labeling and culturing techniques with higher detection sensitivity.

The risk of CMV infection has been found to increase after treatment for acute graft rejection [1, 11, 14-16], and our data confirm this finding. Forty-two of the 86 patients (48.8%) who experienced rejection during the study developed CMV infection. We noted that antecedent rejection was also more common in culture-proven cases than in patients having titer elevations only. Furthermore, 56.3% (9/16) of the patients with isolated titer elevations had antecedent rejection as compared to 76.7% (33/43) with positive cultures. A good number of patients with

positive cultures had two rejection episodes, something which is expected with increased immunosuppression. A large number of patients (54.8%) who developed both rejection and infection received OKT3, but OKT3 per se did not seem to contribute significantly to development of the infection.

With regard to the gancyclovir-treated group, side effects occurred in 8 out of 19 patients. The fact that other medications and antibiotics were administered concurrently with gancyclovir could partly explain the occurrence of these side effects in all but two patients who had seizure and rash while on gancyclovir alone. In comparison, a study of 17 transplant patients (5 kidney and 12 liver transplants) reported side effects to be mainly hematological abnormalities occurring in 4 out of 17 patients. These abnormalities ranged from thrombocytopenia to leukopenia to neutropenia. All reversed after discontinuation of treatment [8]. In spite of the side effects that our patients developed, gancyclovir demonstrated clinical, virological, and serological efficacy in the treated group. An excellent survival rate of 89.5%, with a follow-up of up to 1.5 years, was achieved in the treated group. The survival rate in the untreated group was also high (82.5%). The fact that the treated group had a more severe disease, as evidenced by clinical symptoms, positive CMV

cultures from multiple sites simultaneously, multiple concomitant infections, and concurrent rise in CMV antibody titers demonstrates the efficacy of gancyclovir. The successful treatment of these severe symptomatic infections could be attributed to the combination of gancyclovir with other treatment modalities, in particular the administration of gamma globulin, which was administered to 14 out of 19 patients together with gancyclovir therapy. This combination therapy has been demonstrated to be highly efficacious in other settings as well [2, 17, 18]. Yet, the two patients who died in the treated group were patients who received combination therapy (see Table 1).

Although CMV infection continues to be a major cause of morbidity in liver transplant recipients at our center, it is no longer a major cause of mortality. The excellent results obtained in these patients can be attributed to a number of factors. First, more sensitive techniques allow early and rapid detection of CMV infection. Second, our protocol calls for lower doses of immunosuppression than those previously used. Third, a judicious decrease in immunosuppression leads to survival in most patients. Finally, the use of gancyclovir in the most severely infected patients with disseminated CMV disease, most of whom have concomitant bacterial infections, improves chances for survival, despite the fact that these immunosuppressed transplant recipients, in our series as well as in other series, have the least chance of survival.

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