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Gastrointestinal cytomegalovirus disease in patients with cancer: A two decade experience in a tertiary care cancer center

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Abstract

Although gastrointestinal cytomegalovirus disease (GI-CMVd) is not common in cancer patients, it is associated with high morbidity and mortality. Herein, we review our 2-decade experience with GI-CMVd in such patient population at The University of Texas M.D. Anderson Cancer Center.

Forty-seven patients were identified. Thirty-four patients (72%) had an underlying haematological malignancy, and 18 patients (38%) developed GI-CMVd following hematopoietic stem cell transplantation (HSCT). Nine (25%) of the 36 cancer patients with data available had AIDS. Upper-GI tract involvement was more common in patients with haematological malignancies than in those with solid tumours ($P = 0.02$). Patients with AIDS were more likely to have colonic involvement than were those without AIDS (67% *vs.* 15%, $P = 0.006$), and patients without AIDS were more likely to have gastric involvement (59% *vs.* 11%, $P = 0.01$). The CMV-attributable mortality rate was 42%. Independent predictors of death by multivariate analysis included disseminated CMV and AIDS ($P < 0.01$). The presentation of GI-CMVd varies according to the type of cancer, and AIDS. GI-CMVd is associated with a high mortality among cancer patients, particularly those with disseminated CMV disease or AIDS.

Keywords: Cytomegalovirus; Gastritis; Colitis; HIV; AIDS; BMT; HSCT; Cancer

1. Introduction

Gastrointestinal cytomegalovirus disease (GI-CMVd) is a rare infection that is associated with high morbidity and mortality in immunocompromised patients, especially those with AIDS, autoimmune diseases, chronic renal failure, solid organ transplantation, hematopoietic stem cell transplantation (HSCT), cancer, and recipients of corticosteroid therapy [1–7]. Reports of GI-CMVd in cancer patients have been limited to a few case reports, small case series, and postmortem studies [1–3,6,8–20].

In an effort to determine the incidence of GI-CMVd, the relationship between patient characteristics and features of GI-CMVd, and predictors of death due to GI-CMVd among cancer patients, we have reviewed a 2-decade experience at The University of Texas M.D. Anderson Cancer Center.

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2. Patients and methods

2.1. Patient identification

The microbiology, pathology, and autopsy reports with positive findings for CMV in patients with cancer seen at M.D. Anderson Cancer Center between January 1985 and December 2003 were reviewed to identify patients with GI-CMVd.

CMV in tissue specimens was confirmed in the case of any of the following: histopathologic examination showing viral inclusions suggestive of CMV or positive findings for CMV on immunohistochemical staining, culture (e.g., shell vial centrifugation or conventional viral culture), or *in situ* hybridization.

2.2. Therapy and outcome

Before 1999, patients who were CMV seropositive and had undergone allogeneic HSCT received CMV prophylaxis with ganciclovir (5 mg/kg/d three to five days per week) from engraftment until day 100 after transplantation if they had undergone a T-cell depleted transplants; or unrelated or mismatched related donor transplant; or were receiving systemic corticosteroids. Foscarnet (60 mg/kg/d) was substituted for ganciclovir if myelosuppression occurred during ganciclovir prophylaxis. After 1999, prophylaxis with ganciclovir (5 mg/kg/d five to seven days per week) or foscarnet (60 mg/kg/d) as an alternative in patients with myelosuppression caused by ganciclovir was administered from engraftment until day 90 if they had graft-*vs*.-host disease (GVHD) and were receiving systemic corticosteroids; had undergone a T-cell depleted transplants; had a prior history of CMV infection or disease; and were receiving alemtuzumab. Patients not in the preceding groups were monitored weekly for CMV antigenemia and were preemptively treated with ganciclovir or foscarnet if antigenemia was detected ($\geqslant 3$ cells per 10^6 white blood cells).

Therapy for GI-CMVd consisted of intravenous administration of ganciclovir 5 mg/kg every 12 h, with or without intravenous administration of standard immune globulin (IVIG) 500 mg/kg every other day. Foscarnet was substituted for ganciclovir in patients who experienced severe myelosuppression during ganciclovir therapy. The foscarnet dosage was 60 mg/kg given intravenously every 8 h.

Death was attributed to GI-CMVd if the signs and symptoms of GI-CMVd had not resolved at the time of death, or there was evidence of persistent CMV infection at autopsy.

2.3. Definitions

GI-CMVd was defined as the presence of clinical and endoscopic features of GI disease and evidence of CMV in tissue specimens. CMV infection or disease was defined by the presence of antigenemia or end organ disease, respectively [21].

AIDS was defined according to standard criteria [22]. Coinfections were defined as other infections that occurred within 30 days before, at onset, or after of the episode of GI-CMVd. Neutropenia was defined as a neutrophil count of less than 500/mm^3, and lymphopenia was defined as a lymphocyte count of less than 1000/mm^3. Criteria used to define elevated levels on blood chemistry studies were as follows: creatinine, greater than 1.5 mg/dl; total bilirubin, greater than 1 mg/dl; and lactate dehydrogenase, greater than 618 U/l.

A high dose of corticosteroids was defined as a cumulative dose equal or greater than 600 mg equivalent of prednisone.

Antiviral-associated haematological toxicity was defined as a decrease of at least 50% in the baseline neutrophil count, and antiviral-associated renal toxicity was defined as an increase of at least 50% in the baseline serum creatinine level.

2.4. Statistical analysis

We used frequencies and percentages to summarise patient groups and used Fisher's exact test to analyse the distribution of all groups. Outcome was measured from the day of diagnosis of GI-CMVd until death or last day of follow up. Survival was estimated using the Kaplan–Meier nonparametric method with the log-rank test used to determine statistical significance. Univariate and multivariate Cox proportional hazards regression analyses were conducted to evaluate the crude effects of each potential predictor on GI-CMVd-associated death. All tests were two-sided. Differences were considered statistically significant when $P < 0.05$. Statistical analysis was performed using SPSS version 11.0 statistical software (SPSS Inc, Chicago, IL).

3. Results

3.1. Patient characteristics and incidence of GI-CMVd

From January 1985 through December 2003, 47 of the 236 113 patients with cancer cared for at our institution had GI-CMVd. Clinical characteristics of these patients are presented in Table 1. The incidence of GI-CMVd was 20 cases per 100 000 patients. The majority of patients had haematological malignancies (Table 1). The incidence among patients with haematological malignancies was higher than the incidence among patients with solid tumours (102 cases *vs.* 6 cases per 100 000 patients; $P < 0.001$). There was a trend towards higher incidence of cases during the 1985–1994 period

Table 1
Characteristics of patients with cancer and gastrointestinal cytomegalovirus disease ($n = 47$)

Characteristic	Number (%) of patients[a]
Gender, male/female	28/19
Median age (range)	47 yr (19–77 yr)
Underlying cancer	
Haematological	34/47 (72)
Leukaemia	17 (50)
Lymphoma	15 (44)
Multiple myeloma	2 (6)
Solid tumor	13/47 (28)
Kaposi's sarcoma	4 (31)
Colorectal	2 (15)
Others[b]	7 (54)
HSCT	18/47 (38)
Allogeneic	16 (89)
Autologous	2 (11)
AIDS	9/36 (25)[c]
Type of GI CMV disease	
GI involvement alone	34/47 (72)
Only 1 GI site	27 (79)
More than 1 GI site	7 (21)
Disseminated disease	13/47 (28)
Postmortem diagnosis	5/47 (11)
Median Apache II score at onset of GI CMV disease (range)	13 (5–22)
Absolute neutrophil count $<500/mm^3$ at onset of GI CMV disease	3/46 (7)
Absolute lymphocyte count $<1000/mm^3$ at onset of CMV disease	35/46 (76)
Corticosteroids[d]	28/47 (60)
Corticosteroids $\geqslant 600$ mg of prednisone equivalent[d]	21 (75)
Chemotherapy[d]	32/47 (68)
Death attributable to GI CMV disease[e]	18/43 (42)

AIDS, acquired immune deficiency syndrome; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; GI, gastrointestinal.
[a] In some categories, denominator is less than 47 because of missing data.
[b] One case each of breast cancer, lung cancer, prostate cancer, renal cancer, stomach cancer, leiomyosarcoma, and unknown primary cancer.
[c] Based only on patients with known HIV serostatus.
[d] Within 6 months before onset of GI CMV disease.
[e] Based on number of patients with outcome data available.

compared to 1995–2003 period (26 *vs.* 16 cases per 100 000 patients; $P = 0.07$).

Eighteen (0.2%) of the 6.074 patients who had undergone HSCT had GI-CMVd—allogeneic in 16 patients. The incidence among patients who underwent HSCT was 296 cases per 100 000 patients; the incidence was higher for patients who underwent allogeneic HSCT than for those who underwent autologous HSCT (608 *vs.* 58 cases per 100 000 patients; $P < 0.001$). The incidence among patients who underwent HSCT was stable over the study period. Of the 16 patients who had undergone allogeneic HSCT, 5 (31%) had grade III or IV GVHD, and 6 (38%) had GVHD involving the GI tract.

Several patient characteristics varied according to the underlying condition (Tables 2–5). All 27 patients in whom CMV serologic tests were performed before the onset of GI-CMVd were seropositive. Seven (16%) of 43 patients with data available had had history of CMV antigenemia.

3.2. Time to onset of GI-CMVd

The median time to onset of GI-CMVd after cancer diagnosis was longer in patients with haematological malignancies than in those with solid tumours (Table 2). Among the 18 patients who had undergone HSCT, the median time to onset of GI-CMVd after HSCT was 88 days (range, 17–1099 days). Nine (56%) of the 16 patients who had undergone allogeneic HSCT developed GI-CMVd more than 90 days after HSCT. Six of these 9 patients had GVHD (grade III-IV, and with gastrointestinal involvement in 3 cases, respectively).

3.3. Methods of diagnosis

Forty-two patients underwent GI endoscopy. The most common abnormalities identified were inflammation (24 patients), ulcerations (21 patients), erosions (14 patients), and mucosal hemorrhage (8 patients). Thirty-one patients had more than one abnormality. Three patients had endoscopically normal GI mucosa despite the presence of GI symptoms and microscopic finding of cytomegalic inclusions seen in biopsy specimens. The 5 patients who did not undergo GI endoscopy had GI-CMVd diagnosed by liver biopsy in a patient with GI symptoms (1 patient) or autopsy (4 patients).

In addition to the GI endoscopy, 9 patients had barium radiographs. The most common abnormalities identified were ulcers (3 patients), nodules (2 patients), and obstruction of the GI tract (2 patients). Twenty-one patients had computed tomography of the abdomen and pelvis. The most common abnormalities identified were ascites (7 patients), lymphadenopathy (6 patients), and thickening of the wall of the GI tract (4 patients).

Confirmation of CMV in tissue specimens by various diagnostic methods used was as follows: histopathology (presence of cytomegalic inclusions), 46 (98%) of 47 patients; CMV immunohistochemical staining, 14 (70%) of 20 patients; conventional or shell vial cultures, 5 (71%) of 7 patients; and *in situ* hybridization, 1 of 1 patient.

CMV viremia or antigenemia was detected in 18 (64%) of 28 patients tested by either culture or pp65

Table 2
Sites of involvement in patients with cancer and gastrointestinal cytomegalovirus disease, overall and according to underlying condition

	Total no. of cases	No. (%) of cases by underlying condition			
		Leukaemia ($n = 2$)	Lymphoma ($n = 14$)	Solid tumor ($n = 13$)	HSCT ($n = 18$)
Site[a]					
Esophagus	8	0 (0)	1 (7)	3 (23)	4 (22)
Stomach	24	2 (100)	7 (50)	5 (38)	10 (56)
Duodenum	5	0 (0)	2 (14)	1 (8)	2 (11)
Ileum	1	0 (0)	1 (7)	0 (0)	0 (0)
Colon or rectum	16	0 (0)	5 (36)	8 (62)[b]	3 (17)[b]
Liver	4	0 (0)	1 (7)	1 (8)	2 (11)
Type of Involvement					
More than 1 GI site[c]	5	0 (0)	1 (7)	2 (15)	2 (11)
Disseminated[d]	13	1 (50)	3 (21)	2 (15)	7 (39)

HSCT, hematopoietic stem cell transplantation; GI, gastrointestinal.
[a] Patients may have more than one site involved.
[b] $P = 0.02$.
[c] Other than colon or rectum.
[d] Involving more than 1 organ system.

assay at the discretion of the primary physician. In 12 patients, the onset of viremia or antigenemia preceded the onset of GI-CMVd (median, 9 days; range, 1–296 days), with a median cell count of 17 per 10^6 white blood cells (range, 3–6494 cells per 10^6 white blood cells).

Table 3
Characteristics of patients with cancer and gastrointestinal cytomegalovirus disease according to underlying cancer

Characteristic	No. (%) of patients		
	Patients with haematological cancer ($n = 34$)	Patients with solid tumours ($n = 13$)	P Values
Gender, male/female	17/17	11/2	0.03
Median days to onset of GI CMV disease after cancer diagnosis (range)	706 (0–3068)	74 (4–1023)	0.001
Onset of GI CMV disease <6 months after cancer diagnosis	8/32 (25)	9/13 (69)	0.008
Prior relapse of cancer	18/34 (53)	0/13 (0)	0.001
AIDS	5/31 (16)	4/5 (80)	0.009
Postmortem diagnosis	2/34 (6)	3/13 (23)	0.08
Disseminated CMV disease	11/34 (32)	2/13 (15)	NS
Site of GI involvement			
Upper[a]	25/34 (74)	5/13 (38)	0.02
Lower[b]	6/34 (18)	6/13 (46)	0.02
Both	3/34 (9)	2/13 (15)	NS
Stomach involvement	19/34 (56)	5/13 (38)	NS
Colon involvement	8/34 (24)	8/13 (62)	0.01
Absolute lymphocyte count <1000/mm^3 at onset of GI CMV disease	22/33 (67)	13/13 (100)	0.01
Concomitant CMV antigenemia	18/26 (69)	0/2 (0)	NS
Corticosteroids[c]	23/34 (68)	5/13 (38)	0.06
Corticosteroids ⩾600 mg of prednisone equivalent[c]	17/23 (74)	4/5 (80)	NS
Chemotherapy[c]	24/34 (71)	8/13 (62)	NS
Treatment type			
Single antiviral therapy	7/33 (21)	5/13 (38)	NS
Combination therapy[d]	18/33 (55)	0/13 (0)	0.0007
No therapy	8/33 (24)	8/13 (62)	0.01
Toxicity related to antiviral therapy	16/25 (64)	0/5 (0)	0.01
Death attributable to GI CMV disease[e]	13/32 (41)	5/11 (45)	NS

AIDS, acquired immune deficiency syndrome; CMV, cytomegalovirus; GI, gastrointestinal; NS, not significant.
[a] Esophagus, stomach, and small bowel.
[b] Colon and rectum.
[c] Within 6 months of onset of GI CMV disease.
[d] With either other antiviral drug or intravenous administration of immune globulin.
[e] Based on number of patients with outcome data available.

Table 4
Characteristics of patients with cancer and gastrointestinal cytomegalovirus disease according to the history of hematopoietic stem cell transplantation

Characteristic	No. (%) of patients		
	Patients who had undergone HSCT ($n = 18$)[a]	Non-HSCT patients ($n = 29$)[a]	*P* Values
Gender, male/female	8/10	20/9	0.09
Median age (range)	43 yr (19–59 yr)	50 yr (20–77 yr)	0.03
Prior CMV infection/disease	7/17 (41)	3/26 (12)	0.03
Disseminated CMV disease	7/18 (39)	6/29 (21)	NS
Site of GI involvement			
Upper[b]	14/18 (78)	16/29 (55)	NS
Lower[c]	2/18 (11)	10/29 (34)	0.09
Both	2/18 (11)	3/29 (10)	NS
Stomach involvement	10/18 (56)	14/29 (48)	NS
Colon involvement	3/18 (17)	13/29 (45)	0.05
Median Apache II score at onset of CMV disease (range)	13 (7–19)	13 (5–22)	NS
Absolute lymphocyte count $<1000/mm^3$ at onset of GI CMV disease	14/18 (78)	21/28 (75)	NS
Concomitant CMV antigenemia	12/16 (75)	6/12 (50)	NS
Corticosteroids[d]	14/18 (78)	14/29 (48)	0.04
Corticosteroids $\geqslant$ 600 mg of prednisone equivalent[d]	12/14 (86)	9/14 (64)	NS
Treatment type			
Single antiviral therapy	3/18 (17)	9/28 (32)	NS
Combination therapy[e]	12/18 (67)	6/28 (21)	0.002
No therapy	3/18 (17)	13/28 (46)	0.04
Median days of therapy (range)	21 (8–110)	20 (9–59)	NS
Toxicity related to antiviral therapy	12/15 (80)	4/15 (27)	0.003
Death attributable to GI CMV disease[f]	6/17 (35)	12/26 (46)	NS

CMV, Cytomegalovirus; HSCT, hematopoietic stem cell transplantation; GI, gastrointestinal; NS, not significant.
[a] Percentages may not equal 100 due to rounding.
[b] Esophagus, stomach, and small bowel.
[c] Colon and rectum.
[d] Within 6 months of onset of GI CMV disease.
[e] With either other antiviral drug or intravenous administration of immune globulin.
[f] Based on number of patients with outcome data available.

3.4. Symptoms of GI-CMVd at diagnosis

All patients were symptomatic at the time of diagnosis, mainly with fever (72%), nausea or vomiting (62%), abdominal pain (55%), and diarrhoea (53%). Fever at diagnosis was more common in patients with upper-GI-tract GI-CMVd than in those with lower-GI-tract GI-CMVd (83% *vs.* 50%, $P = 0.02$). Conversely, diarrhoea at diagnosis was more common in patients with lower GI-CMVd than in those with upper GI-CMVd (75% *vs.* 36%, $P = 0.02$). Twenty-four patients (51%) had concurrent GI bleeding. GI bleeding was more common in patients with lower GI-CMVd than in those with upper GI-CMVd (75% *vs.* 40%, $P = 0.04$). The duration of symptoms was similar in patients with lower and upper GI-CMVd. Seventeen patients (36%) were admitted to the intensive care unit (ICU).

Lymphopenia was the most common haematological abnormality identified (Table 1).

3.5. Concurrent and prior medical conditions

Nine (25%) of the 36 cancer patients tested for HIV infection, had AIDS, defined by either a $CD4^+$ T-cell count lower than $200/mm^3$ or the presence of AIDS-defined events (e.g., lymphoma or Kaposi's sarcoma). Among patients with AIDS, the median $CD4^+$ T-cell count at onset of infection was $22/mm^3$ (range, 1–$242/mm^3$), and 86% of patients had a CD4+ T-cell count lower than $200/mm^3$. Most of the AIDS patients had non-Hodgkin's lymphoma (56%). Two patients required abdominal surgery for small-bowel perforation. Both had AIDS and diffuse large cell lymphoma involving the small bowel.

Prior to the onset of GI-CMVd, 27 patients (57%) had structural damage of the GI tract due to either cancer (e.g., stomach cancer, colon cancer, lymphoma) or non-malignant disease (e.g., diverticular disease, GVHD, peptic ulcer disease, inflammatory bowel disease).

Table 5
Characteristics of patients with cancer and gastrointestinal cytomegalovirus disease according to the presence or absence of AIDS ($n = 36$)[a]

Characteristic	No. (%) of patients		
	Patients with AIDS ($n = 9$)	Patients without AIDS ($n = 27$)	*P* Values
Gender, male/female	9/0	13/14	0.006
Underlying cancer			
Haematological	5/9 (56)	26/27 (96)	0.009
Solid tumor	4/9 (44)	1/27 (4)	
Cancer involving the GI tract	5/9 (56)	6/27 (22)	0.09
Active cancer	9/9 (100)	15/27 (56)	0.01
Prior relapse of cancer	0/9 (0)	17/27 (63)	0.001
Median days to onset of GI CMV disease after cancer diagnosis (range)	77 (0–947)	711 (44–2581)	0.001
Disseminated CMV disease	2/9 (22)	8/27 (30)	NS
Site of GI involvement			
Upper[b]	3/9 (33)	22/27 (81)	0.01
Lower[c]	6/9 (67)	3/27 (11)	0.002
Both	0/9 (0)	2/27 (7)	NS
Stomach involvement	1/9 (11)	16/27 (59)	0.01
Colon involvement	6/9 (67)	4/27 (15)	0.006
Median Apache II score at onset of GI CMV disease (range)	11 (5–14)	13 (7–19)	0.01
Co-morbid conditions	1/9 (11)	15/27 (56)	0.02
GI co-infection within 1 month of onset of GI CMV disease	5/9 (56)	4/27 (15)	0.02
Corticosteroids[d]	3/9 (33)	19/27 (70)	NS
Prior radiotherapy	2/9 (22)	17/27 (63)	0.05
Chemotherapy[d]	4/9 (44)	21/27 (78)	0.09
Treatment type			
Single antiviral therapy	4/9 (44)	6/27 (22)	NS
Combination therapy[e]	1/9 (11)	16/27 (59)	0.01
No therapy	4/9 (44)	5/27 (19)	NS
Toxicity related to antiviral therapy	0/5 (0)	14/22 (64)	0.01
Death attributable to GI CMV disease[f]	4/7 (57)	7/25 (28)	NS

AIDS, acquired immune deficiency syndrome; CMV, cytomegalovirus; GI, gastrointestinal; NS, not significant.
[a] Based only on patients with known HIV serostatus.
[b] Esophagus, stomach, and small bowel.
[c] Colon and rectum.
[d] Within 6 months of onset of GI CMV disease.
[e] With either other antiviral drug or intravenous administration of immune globulin.
[f] Based on number of patients with outcome data available.

Thirty-four patients (72%) had coinfections. The most common were bloodstream infections (in 14 patients, 12 of whom had bacteremia mainly due to gram positive cocci), gastrointestinal infections (in 10 patients, mainly caused by *Clostridium difficile* toxin in 3 patients, adenovirus in 2, herpes simplex virus in 2), and pulmonary infections (in 9 patients, 6 of whom had mold infections).

Twenty-eight patients (60%) received systemic corticosteroids within 6 months before the onset of GI-CMVd; 21 of these patients (75%) received a high dose of corticosteroids.

Prior use of corticosteroids was more common in HSCT recipients than patients who did not undergo HSCT (Table 4). Thirty-two (68%) patients received chemotherapy within 6 months before the onset of GI-CMVd (Table 1).

3.6. Infection site according to type of underlying cancer and patient characteristics

Most patients (64%) had upper-GI-tract involvement. The most common sites affected by GI-CMVd were the stomach (41%) the colon and rectum (28%) (Table 2).

The sites involved by CMV varied according to the underlying cancer (Tables 2–5). Colorectal involvement was more common in patients with solid tumours than in those who underwent HSCT (Table 2). Upper-GI tract-involvement was more common in patients with haematological malignancies than in those with solid tumours (Table 3). Colonic involvement was more common in patients with AIDS than in those without AIDS, and gastric involvement was more common in patients without AIDS than in those with AIDS (Table

5). All patients with AIDS in the setting of an underlying solid tumor had lower-GI-tract CMVd.

Thirteen patients (28%) had disseminated CMV infection diagnosed either at onset of infection (in 5 patients) or on autopsy (in 8 patients) (Tables 1 and 2). The sites of dissemination were mainly the lungs (12 patients; documented by CMV in bronchoalveolar lavage specimens or on autopsy, in 6 patients each), and adrenal glands (in 6 patients, all documented by autopsy). When compared to patients with GI-tract-localised disease, dissemination was significantly associated with liver involvement; admission to the ICU; use of mechanical ventilation; high total bilirubin level; high lactate dehydrogenase level; prior use of corticosteroids, cyclophosphamide, thiotepa, cyclosporine, or zolimomab (monoclonal antibody against CD5); and development of antiviral toxicity (all $P < 0.05$).

3.7. Therapy and outcome

Antiviral therapy was administered to 30 (64%) out of 47 patients. The majority of patients (18 patients or 60%) were treated with combination of antiviral agents or an antiviral agent and IVIG. The combinations were ganciclovir plus IVIG (in 6 patients); foscarnet plus IVIG (in 5 patients); ganciclovir plus foscarnet plus IVIG (in 5 patients); ganciclovir plus foscarnet (in 1 patient); foscarnet plus cidofovir (in 1 patient). Combination therapy was more common in patients with haematological malignancies than in those with solid tumours, however such a treatment modality did not affect the outcome of GI-CMVd (Table 2). Among the 12 patients who did not received combination therapy, 9 received ganciclovir and 3 received foscarnet as initial therapy.

The median duration of antiviral therapy was 21 days (range, 8–110 days). The median duration of symptoms after the initiation of antivirals was 18 days (range, 3–79 days). Sixteen of the 30 patients developed common antiviral-associated toxicities (haematological toxicity in 11 patients, nephrotoxicity in 3, and both side effects in 2). The incidence of antiviral toxicity was similar in patients who received more than one antiviral compared to those who received monotherapy. Treatment characteristics such as median duration of therapy, and early initiation of antivirals (administered within 24 h of diagnosis) were similar in patients who died due to GI-CMVd compared to those who survived.

Data on outcome was available for 43 of the 47 patients. Eighteen (42%) of these 43 patients died of GI-CMVd. Mortality rate was higher in patients who did not receive antiviral therapy (Table 6, Fig. 1A). Among the 14 patients with outcome data who did not receive antiviral therapy, 9 died of GI-CMVd; 4 patients were not treated because the diagnosis only became known postmortem. The 9 patients who did not receive antivirals and died of GI-CMVd were less likely to have endoscopically documented inflammation (0% *vs.* 80%; $P = 0.01$) compared to the 5 non-treated patients who survived.

Predictors of death due to GI-CMVd by univariate and multivariate analysis are shown in Table 6. The likelihood of surviving GI-CMVd was 10 times as high in patients with localised CMV to the GI tract as in patients with disseminated CMV disease. Likewise, the likelihood of surviving GI-CMVd was 20 times as high in patients without AIDS as in patients with AIDS (Table 6). Kaplan–Meier survival curves for patients with GI-CMVd are depicted in Fig. 1.

4. Discussion

Our study describes a large cohort of cancer patients with GI-CMVd, an entity rarely reported in this patient population (Table 7). We did not find an increase in the incidence of GI-CMVd over the last decade, despite the

Table 6
Predictors of fatal outcome of patients with cancer and gastrointestinal cytomegalovirus disease ($n = 43$)

Characteristic	No. (%) of patients[a]		Univariate	Multivariate	Hazard ratio	95% CI
	Patients who died of GI-CMVd ($n = 18$)	Patients who did not die of GI-CMVd ($n = 25$)				
AIDS	4/11 (36)	3/21 (14)	0.003	0.002	20.01	(2.88–138.96)
Disseminated CMV disease	11/18 (61)	1/25 (4)	0.006	0.002	10.04	(2.36–42.612)
Absolute lymphocyte count $<1000/mm^3$ at onset of GI-CMVd	16/18 (89)	16/24 (67)	0.03	0.110	13.05	(0.56–303.91)
Elevated creatinine	9/18 (50)	4/25 (16)	0.03	0.393	3.95	(0.66–23.37)
Elevated total bilirubin	11/18 (61)	5/25 (20)	0.01	0.111	1.08	(0.98–1.18)
Elevated lactate dehydrogenase	14/18 (78)	12/25 (48)	0.07	0.647	0.54	(0.04–7.33)
Antiviral treatment	9/18 (50)	19/24 (79)	0.01	0.114	9.88	(0.57–168.60)
Toxicity related to antiviral therapy	7/8 (88)	9/19 (47)	0.006	0.755	1.09	(0.12–9.38)

AIDS, acquired immune deficiency syndrome; CI, confidence interval; CMV, cytomegalovirus; GI-CMVd, gastrointestinal cytomegalovirus disease.
[a] Includes 5 patients with postmortem diagnosis of GI-CMVd.

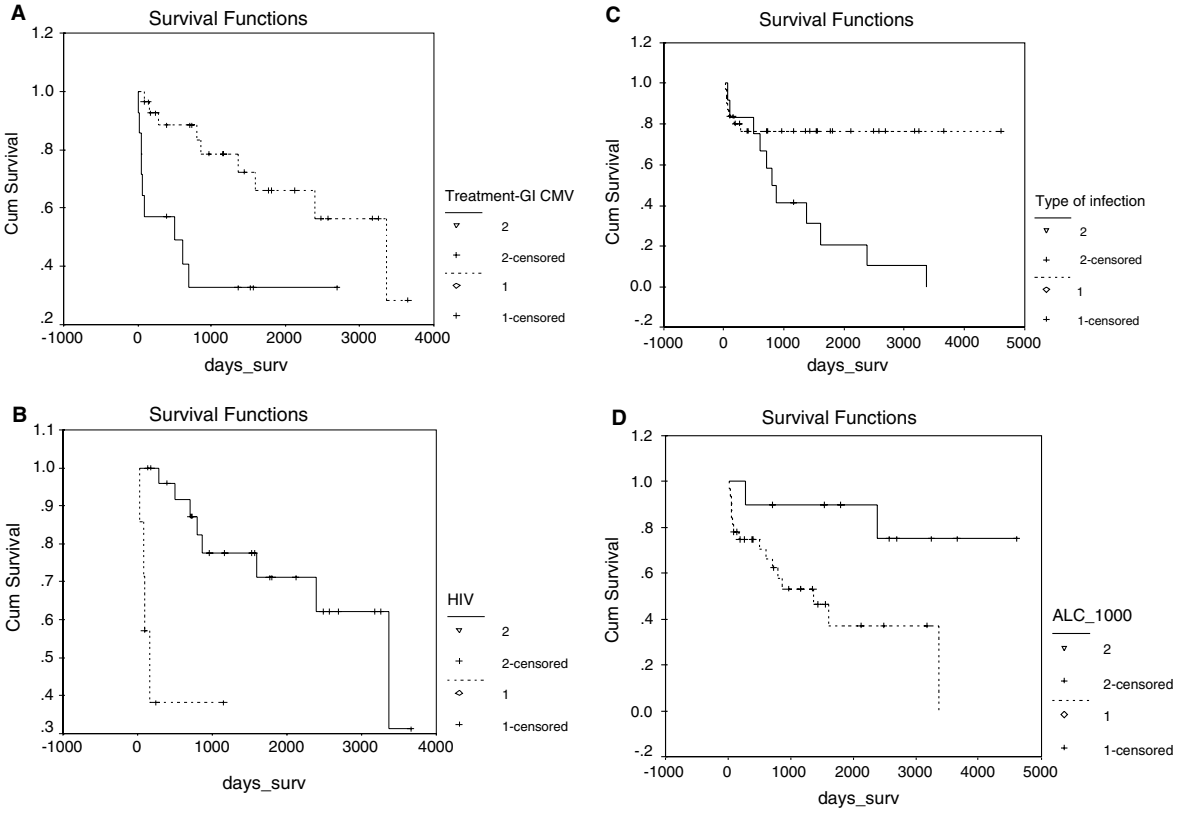

Fig. 1. Kaplan–Meier survival curve for patients with gastrointestinal cytomegalovirus disease (GI-CMVd). (A) Effect of antiviral treatment ($P < 0.01$). Dotted line: patients who received antiviral treatment. Solid line: patient who did not receive antivirals. (B) Effect of AIDS ($P < 0.001$). Dotted line: patients with AIDS. Solid line: patients without AIDS. (C) Effect of disease dissemination ($P < 0.001$). Dotted line: patients with CMVd limited to the GI tract. Solid line: patients with disseminated CMV disease. (D) Effect of lymphopenia (absolute lymphocyte count <1000/mm^3) at onset of GI-CMVd ($P = 0.01$). Dotted line: patients with lymphopenia. Solid line: patients without lymphopenia.

increasing number of cancer patients and HSCT recipients seen at our institution over that time. This finding contrasts with reports from our institution of a steady increase during the same period in the rate of CMV pneumonia [23–25], the most common manifestation of CMV disease in cancer patients [1,2,18]. This discrepancy might reflect a more sensitive culture methods for diagnosing CMV pneumonia (i.e., shell vial culture in bronchoalveolar lavage), an overdiagnosis of CMV pneumonia, which is rarely confirmed histopathologically in cancer patients, or an underdiagnosis of GI-CMVd.

In our series, the higher incidence of GI-CMVd among patients with haematological malignancies might be due primarily to a higher degree of immunosuppression in these patients. Interestingly, the incidence of GI-CMVd in our HSCT recipients was significantly lower than the incidence reported from another transplant center [26] (18 of 6074 HSCT recipients at our institution *vs.* 46 of 2240 HSCT recipients at the other center; $P < 0.001$). This finding might be a result of differences between the 2 institutions in CMV prophylaxis, CMV surveillance, preemptive therapy against CMV, and/or a more aggressive approach in diagnosing GI-CMVd in the other institution.

We found that the site of involvement of the GI tract by CMV varied according to the type of cancer. Our findings differ from those of other authors, who found that the location of the GI lesions was similar regardless of the cause of the host's immunodeficiency or the underlying cancer [2,3,15].

CMV frequently involved the GI-tract in patients with AIDS with an estimated incidence of about 30% before the era of highly active antiretroviral therapy (HAART) [27,28], with no reported data in the HAART era. GI-CMVd is also a major cause of mortality in AIDS patients [1,28,29]. They can have CMV-d of any site in the gastrointestinal tract [1], although infection of the lower intestinal tract occurs most commonly [27,30–32]. In our study, all patients with AIDS and solid tumours had lower-GI-tract CMVd. An autopsy study performed before the AIDS epidemic described the upper GI tract as the most common site of GI-CMVd in solid tumor patients [15]. Our data, taken together with this previous study, suggest that CMV infection in the presence of AIDS affects different sites of the GI tract in solid tumor patients. On the other hand, we found that the presence of AIDS may affect the outcome of cancer patients with GI-CMVd. Hence, the presence of

Table 7
Reported case series of GI-CMVd in non-HSCT cancer patients[a]

First author [reference]	Year of publication	No. of patients studied	Predominant underlying cancer (%)	Predominant site of infection (%)	Specific sites of infection (%)	Steroid therapy	Antiviral treatment	Outcome
Rosen [15]	1971	6	Haematological (67%) (lymphoma in 3 cases)	Upper-GI tract[b] (100%)	Stomach (50%), duodenum (50%)	Yes	No	Postmortem series
Rosen [14]	1973	3	Solid tumours (100%) (HCC, sarcoma, and desmoid tumor each in 1)	Upper-GI tract[b] (100%)	Stomach (33%), small intestine (33%), and esophagus + stomach + small intestine (33%)	Yes	No	Postmortem series
Henson [3]	1972	4	Haematological (50%) (leukaemia and MM each in 1 case)	Upper-GI tract[b] (75%)	Stomach (25%), duodenum (25%), esophagus + stomach + ileum + colon (25%), and small intestine (25%)	Yes	No	Postmortem series
Goodman [20]	1979	3	Haematological (100%) (lymphoma in 2 cases)	Lower-GI tract[c,d] (100%)	Colon (100%)	Yes	No	Not reported
Hinnant [40]	1986	3	Haematological (100%) (leukaemia, lymphoma, and MM each in 1 case)	Upper-GI tract[b] (100%)	Not reported	Not reported	Not reported	Not reported
Iwasaki [2]	1987	4	Haematological (50%) (leukaemia and lymphoma each in 1 case)	Upper-GI tract[b] (50%)	Esophagus + stomach (50%), esophagus + stomach + small intestine + colon (25%), esophagus + colon (25%)	Yes	No	Postmortem series
Present report	2005	29	Haematological (55%) (lymphoma in 14 cases)	Upper-GI tract[b] (55%)	Stomach (38%), colon–rectum (35%)		GCV and foscarnet in 10 and 5 patients, respectively	46% Mortality

GI-CMVd, gastrointestinal CMV disease; HCC, hepatocellular carcinoma; HSCT, hematopoietic stem cell transplantation, MM, multiple myeloma.
[a] Case reports were excluded.
[b] Esophagus, stomach, and small bowel.
[c] Colon and rectum.
[d] Study of patients with colonic perforation.

Table 8
Reported case series of GI-CMVd in HSCT recipients[a]

First author [reference]	Year of publication	No. of patients studied	Predominant HSCT (%)	Median days to onset of GI CMVd after HSCT (range)	Specific sites of infection (%)	Antiviral treatment[b]	Overall outcome (%)	Death related to GI-CMVd (%)
Lepinski [43]	1990	3	Allogeneic (100%)	54 (53–110)	Ileum (100%)	GCV in 3 patients	0% mortality	0%
Meyers [33]	1990	74	Allogeneic (100%)	Not reported	Esophagus (46%), duodenum or small intestine (35%)	Not reported	Not reported	Not reported
Reed [34]	1990	37 (divided in 2 groups, GCV *vs.* placebo)	Allogeneic (95%)	Group 1, 63 (32–100); Group 2, 76 (38–162)	Esophagus (50%), stomach (23%), duodenum (23%)	GCV in 18 patients	Not reported	Not reported
Wingard [44]	1990	5	Allogeneic (80%)	40 (17–106)	Not reported	Not reported	Not reported	Not reported
Boeckh [45]	1992	3	Allogeneic (100%)	55 (46–69)	Not reported	Not reported	Not reported	Not reported
Goodrich[46]	1993	8	Allogeneic (100%)	60 (45–74)	Not reported	Not reported	Not reported	Not reported
Boeckh [47]	1995	3	Autologous (100%)	49 (38–55)	Esophagus (66%), rectum (33%)	GCV in 2 patients	0% Mortality	0%
Ljungman [48]	1998	33 (divided in 2 groups, GCV *vs.* IVIG)	Allogeneic (100%)	Group 1, 62 (18–194); Group 2, 69 (34–369)	Not reported	GCV and foscarnet in 28 and 5 patients, respectively	52% Mortality	24%
Crippa [49]	2001	5	Allogeneic (100%)	76 (27–287)	Esophagus plus duodenum (40%), esophagus (20%), stomach (20%)	GCV and foscarnet in 3 and 1 patient, respectively	80% Mortality	0%
van Burik [26]	2001	46	Allogeneic (96%)	91 (17–527)	Esophagus and/or stomach and/or intestine (76%)	GCV and foscarnet in 43 and 1 patient, respectively	67% Mortality	23%
Present report	2005	18	Allogeneic (88%)	88 (17–1099)	Stomach (48%), esophagus (19%)	GCV and foscarnet in 8 and 7 patients, respectively	71% Mortality	35%

GI-CMVd, gastrointestinal CMV disease; GCV, ganciclovir; HSCT, hematopoietic stem cell transplantation.
[a] Case reports were excluded.
[b] As initial antiviral therapy with or without IVIG.

GI symptoms in a patient with cancer and AIDS should prompt an early evaluation for GI-CMVd.

GI-CMVd is a well-documented infection in patients who have undergone HSCT (Table 8). We found that the stomach was the most common site of GI-CMVd in our HSCT patients. In contrast, two large series in such a patient population identified the esophagus as the predominant site of CMV infection [33,34].

In our series, CMV antigenemia was not infrequently observed. Real-time polymerase chain reaction (PCR) for detection of CMV-DNA in the blood is an alternative method that is also rapid and sensitive for diagnosing active disease; additionally, it appears to be more sensitive than the identification of antigenemia in detecting CMV reactivation in patients with haematological malignancies and those who have undergone HSCT [35,36]. The usefulness of quantitative CMV viral load measurements in peripheral blood of patients with GI-CMVd needs to be explored. The sensitivity and specificity of culture compared with histopathology for confirmation of GI-CMVd in tissue specimens is controversial [1]. We found positive tissue cultures for CMV in almost 70% of biopsy specimens that had positive CMV viral inclusions, immunohistochemical staining, or *in situ* hybridization, which contrasted with the approximately 20% concordance between tissue culture and histopathology previously reported for HSCT recipients [37]. In HIV-infected patients, PCR amplification of CMV DNA from biopsy specimens has been used for early detection of GI-CMVd [38], and this approach might be implemented in cancer patients. Indeed, early diagnosis in both cancer patients in general and cancer patients who have undergone HSCT allows early initiation of antiviral therapy that may alter the clinical course and prevent complications such as intestinal perforation or dissemination [7,39]. Oropharyngeal excretion of CMV seems to be predictor for GI-CMVd in HSCT patients [33]. Furthermore, identification of CMV DNA in stool samples appears to be helpful in diagnosing GI-CMVd in AIDS patients [8]. The role of such diagnostic methods in cancer patients needs to be determined.

The use of antivirals in patients with GI-CMVd has been debated. For instance, spontaneous remission of GI-CMVd has been documented in few cancer patients and those who have undergone HSCT [2,33,40]. In addition, a randomised, placebo-controlled trial of ganciclovir in the treatment of HSCT patients with GI-CMVd showed virologic but not clinical benefit [34]. However, that particular study evaluated mainly patients with upper-GI-tract CMVd treated with a relatively low dose (2.5 mg per kg 3 times a day) of ganciclovir for a short period (14 days). On the other hand, many other uncontrolled trials in solid organ transplant recipients, HSCT recipients, and patients with AIDS have demonstrated the benefit of antiviral therapy for treating GI-CMVd [26,28,39,41,42]. Given the efficacy of antiviral therapy in such studies as well as the improve survival observed in our treated patients although small number, (Fig. 1A) the use of antiviral treatment is recommended in cancer patients and HSCT recipients with GI-CMVd, especially among those who are unable to mount an immune response against CMV.

The limitations of our study is its retrospective nature with a heterogeneous population of cancer patients, and our results may reflect the composition of the patient population assessed. In addition, follow-up biopsy specimens were not available in some patients, and the outcome of such patients was assessed on clinical grounds. However, it has been reported that in immunocompromised patients with GI-CMVd, the clinical improvement does not always correlate with the histopathologic response observed in follow-up biopsy specimens [6].

In summary, in this large cohort of cancer patients with GI-CMVd, the presentation of GI-CMVd varied according to the type of cancer, history of HSCT, and AIDS. GI-CMVd is associated with a high mortality rate among patients with cancer, particularly those with disseminated CMV disease or AIDS.

Conflict of interest statement

None declared.

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