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Cytomegalovirus (CMV) resistance in CD34⁺ selected hematopoietic cell transplant (HCT) recipients

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Abstract

Background—Cytomegalovirus (CMV) viremia after CD34⁺ selected hematopoietic stem cell transplant (HCT) often requires prolonged antiviral therapy. We report rates and outcomes of resistant CMV in a contemporary cohort of CD34⁺ selected HCT recipients managed preemptively.

Methods—We retrospectively reviewed 220 consecutive, CMV seropositive recipients (R+), who received CD34⁺ selected HCT at Memorial Sloan Kettering Cancer Center between June 2010 and December 2014. Patients were monitored by quantitative CMV PCR and were treated preemptively. CMV resistance was tested by a genotypic assay.

Results—161 (73%) patients developed CMV viremia and 47 (29% of viremic and 21% of total patients) had CMV resistance testing by one-year from HCT. CMV resistance was confirmed in 19 (12% of viremic and 9% of total) patients and was identified >3months from HCT in 90% of patients. Twelve patients had mutations in UL97 only; the remaining 7 patients had mutations in UL54 only or UL54 and UL97. By 1 year from HCT, 11 of 19 (58%) patients with mutations had CMV end-organ disease. CMV-related mortality in patients with resistance was 42%.

Conclusions—9% of CMV R+, CD34⁺ selected HCT recipients had resistant CMV by 1 year from HCT. Of 19 patients with resistant CMV, 58% had CMV end-organ disease and 42% died of CMV. Effective strategies for CMV prevention and restoration of CMV immunity are needed for CD34⁺ selected HCT.

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Potential conflicts: GAP has been an investigator for Shire, Merck, Chimerix and Astellas and has received consulting fees from Shire, Merck, Chimerix and Astellas.

Keywords

Cytomegalovirus (CMV); Resistance; Genotype; CD34⁺ selected; Hematopoietic stem cell transplantation

Introduction

CMV resistance after conventional hematopoietic stem cell transplant (HCT) is relatively uncommon, ranging from 1-5%.¹ Higher rates (6-10%) have been reported after haploidentical HCT or in pediatric recipients of mismatched allografts.¹⁻³ Prolonged, subtherapeutic levels of antivirals and persistent CMV replication have been associated with emergence of CMV resistance.⁴⁻⁶ Current treatment options for resistant CMV are limited and carry substantial toxicities.⁷⁻⁹ Furthermore, CMV resistance has been associated with increased morbidity and mortality.¹⁰⁻¹³

Approximately 70% of CMV seropositive recipients (R+) of CD34⁺ selected allografts develop CMV viremia with a median onset of 28 days from HCT. Prolonged antiviral therapy is often required for viral suppression until immune reconstitution.¹⁴ Rates of CMV resistance are not well defined in this population. In this retrospective study, we examined 1) the frequency and types of CMV resistance mutations; and 2) outcomes of resistant CMV after CD34⁺ selected HCT.

Methods

Patients

A retrospective review was performed on 220 CMV R+ patients who underwent first CD34⁺ selected HCT at Memorial Sloan Kettering Cancer Center (MSKCC) between June 2010 and December 2014. Patients were followed until death, second HCT, or 1 year from HCT, whichever occurred first. Clinical, laboratory and pharmacy data were extracted from medical records and hospital databases. The study was reviewed and approved by the MSKCC Institutional Review Board, and was granted a waiver of authorization (WA0020-15).

Transplant procedures

Graft manipulation and conditioning regimens have been previously described.¹⁴ *Ex vivo* T-cell depletion was performed by the CliniMACS® CD34⁺ Reagent System (Milenyi, Biotec, Gladbach, Germany). Patients received conditioning with one of the following preparative regimens: busulfan/melphalan/fludarabine, total body irradiation/thio-TEPA/cyclophosphamide, or clofarabine/thio-TEPA/melphalan. Ninety percent were myeloablative.¹⁵ All patients received antithymocyte globulin as part of the conditioning.

Supportive care

Supportive care was provided per the MSKCC standards of care.¹⁴ All patients received standard antiviral prophylaxis with acyclovir for the first year from HCT. CMV R+ was routinely monitored by quantitative PCR in whole blood or plasma twice weekly starting on

day +14 until discharge, at least weekly through day +100; at least once every 2 weeks through day +180 and at least monthly up to 1 year from HCT. Preemptive CMV treatment was initiated for a CMV viral load (VL) $\geq 1,000$ copies/mL in whole blood, VL ≥ 300 IU/mL in plasma samples, or increasing CMV VL trend in consecutive measurements. Standard induction treatment doses were administered until CMV VL was undetectable or detected at stable low level in several consecutive measurements followed by maintenance doses through weeks +12 from HCT or longer at clinician discretion. Valganciclovir (GCV) was used as first line therapy for CMV viremia. Ganciclovir (GCV) was used for patients unable to tolerate oral intake or for concerns of adequate absorption. Foscarnet (FOS) was used in patients with cytopenia or other contraindication to GCV. During parts of the study period brincidofovir (BCV, CMX001) or Maribavir (MBV) was accessible through the clinical trials NCT01143181 and NCT01611974 respectively ([ClinicalTrials.gov](https://clinicaltrials.gov)). In addition to antivirals, donor derived or third party-derived CMV specific cytotoxic T-cells (CTLs) were available through clinical trials at MSKCC. Resistance testing was at the discretion of the treating physician. In general, resistance testing was requested for rising CMV VL after 2 weeks of induction therapy, rising VL after initial response, or VL $\geq 1,000$ IU/mL after 4-6 weeks of CMV antivirals.

Laboratory methods

Since March 18, 2013, the Roche Amplicor PCR was used for routine CMV monitoring in plasma. The lower limit of detection was 81 IU/mL and the linear range of quantitation 137-9,100,000 IU/mL. Prior to March 18, 2013, a home brewed assay was used for CMV monitoring in whole blood. The range of quantitation was 500-1,000,000 copies/mL.¹⁶ CMV genotypic resistance testing was performed by Viracor Eurofins (Lee's Summit, MO). Results were reported as location and type of amino-acid substitution of point mutations in CMV UL97 and UL54 genes and resistance to antivirals.

Definitions

CMV viremia was defined as ≥ 1 positive PCR value above the lower limit of quantitation of the CMV assay used for monitoring. Persistent CMV viremia was defined as CMV VL $\geq 1,000$ IU/mL after 3 weeks of induction dose CMV antivirals. Maximum CMV VL was defined as the highest CMV VL detected by CMV PCR prior to day +180 from HCT or resistance testing, whichever occurred first. Resistant CMV was defined as the presence of resistance mutation through day +365. Early CMV resistance was defined as CMV resistance test positive ≤ 100 days from transplant and late CMV resistance test was defined as CMV resistance test positive >100 days from transplant. Patients with suspected CMV end-organ disease underwent diagnostic procedures to establish the diagnosis unless medically contraindicated. For CMV end-organ disease only proven or probable cases are included.¹⁷ Diagnosis of proven CMV end-organ disease required documentation of CMV in tissue from the relevant organ by histopathology or immunohistochemistry except for CMV retinitis where symptoms and/or signs were sufficient for the diagnosis of proven disease. Diagnosis of probable CMV encephalitis or ventriculitis, detection of CMV in cerebrospinal fluid by CMV PCR without visible contamination of blood ("bloody tap") plus abnormal imaging results or evidence of encephalitis on electroencephalography in addition to compatible clinical symptoms. Probable CMV pneumonitis was defined as the detection of

CMV by quantitation of CMV DNA in bronchoalveolar lavage fluid combined with clinical symptoms and/or signs of pneumonia.

Statistical analysis

Categorical and continuous variables were compared using Chi-square/Fisher's exact test and Mann-U-Whitney test, respectively. All statistical analyses were completed using SAS 9.4 (SAS Inc., Cary, NC). All tests were two-tailed and a *P* value of <0.05 was deemed statistically significant.

Results

Incidence of resistant CMV

Table 1 shows the baseline characteristics of the 220 CMV R+ patients. One hundred and sixty one (73%) patients developed CMV viremia with a median onset of 28 days from HCT (interquartile range [IQR] 23-34; range 14-83). After 2 weeks of preemptive therapy, 58% of patients had VL <1,000 IU/mL and after 3 weeks of preemptive therapy, 30% had VL <1,000 IU/mL (Figure 1).

Overall 47 patients underwent CMV resistance testing. Nineteen patients (8.6%) had 1 resistance mutation identified. The positive diagnostic yield of CMV resistance testing was 40.4% (19 of 47 patients tested had confirmed mutations).

Characteristics of patients tested for CMV resistance

Table 2 shows the virological characteristics of the 47 patients who had CMV resistance tests. Of 47 patients, 19 patients were positive with CMV resistance mutations. Sixteen (84%) patients had UL97 mutations including 12 patients with UL97 only mutations and 4 patients with UL97 and UL54 mutations. The remaining 3 patients had UL54 mutations only.

Compared to patients without mutations, more patients with mutations had CMV VL >1,000 IU/mL after 6 weeks of antiviral therapy (*P* < 0.001). Patients with mutations also had longer duration of CMV VL >5,000 IU/mL (*P* < 0.001). The maximum CMV VL and VL at the time of resistance testing were similar between the 2 groups.

Anti-viral exposure prior to resistance testing for the 19 patients with confirmed mutations is summarized in Table 3. Of the 12 patients with mutations in UL97, 6 (50%) patients had received only GCV for a median of 78 days (range 12-119, IQR 71-74). Five (42%) patients had received GCV for a median of 103 days (range 16-158, IQR 100-130) followed by FOS for 14 days (range 3-34, IQR 12-34) before testing for CMV resistance. One patient had received GCV, FOS and cidofovir (CDV). In the 7 patients with UL54 mutations, GCV and FOS were given for a median of 59 days (range 3-182, IQR 32-73) and 61 days (range 0-71, IQR 26-70), respectively.

Clinical outcomes of resistant CMV

Twenty-one of 220 CMV R+ recipients (10.4%) developed CMV disease by 1 year from HCT. CMV resistance mutations were confirmed in 11 of the 21 patients with CMV disease. Of 19 patients with confirmed mutations, 11 patients had CMV disease (Table 3).

Figure 2 shows CMV VLs over time and outcomes for 2 patients with resistance mutations. Patient #10 (Figure 2a) developed breakthrough CMV viremia with GCV resistant CMV after prolonged suppression with GCV. After a course of FOS and CMV CTLs, he was enrolled in the MBV trial for resistant/refractory CMV.¹⁸ After initial virologic response, he developed fatal CMV encephalitis.

Patient #18 (Figure 2b) was treated with a prolonged course of FOS followed by GCV and concomitant BCV for adenovirus (ADV).¹⁹ After resistance to GCV and CDV were identified, the patient received FOS, however eventually she expired from CMV pneumonitis.

Lymphocyte counts

Of the 19 patients with CMV resistance, 5 had early CMV resistance and 14 had late CMV resistance. Patients with late CMV resistance had lower absolute lymphocyte counts (ALC), as well as lower CD4⁺ and CD8⁺ lymphocyte counts at +180 days from HCT compared to patients with early CMV resistance: late CMV resistance (ALC 0.95 [0.3-1.5], CD4⁺ 18.5 [IQR 0.5-81] and CD8⁺ 17.5 [4-193]/mm³) vs early CMV resistance (ALC 1.7 [0.8-180], CD4⁺ 126 [IQR 26-190] and CD8⁺ 450 [119-741]/mm³).

Discussion

We describe rates and outcomes of resistant CMV in a large contemporary cohort of adult, CMV R+ recipients of CD34⁺ selected HCT after myeloablative or reduced intensity conditioning. The CliniMACS system used for CD34⁺ selection achieves an approximate 3-5 log¹⁰ depletion of CD3⁺ cells with patients receiving ~10³⁻⁴ CD3⁺/kg weight or less.²⁰ Our patients were monitored for CMV by PCR and managed preemptively. CMV resistance testing was at the clinicians' discretion. Confirmed resistance mutations were identified in 19 (9%) patients at 1 year from HCT. Similar rates have been recently reported for haploidentical HCT.³ CMV resistance mutations were identified >100 days from HCT in 74% (14/19) of cases and a median of 114 (IQR 72-140) days of CMV antiviral therapy. Fifty percent of patients with CMV resistance mutations had CMV VL 1000 IU/mL for 6 weeks of preemptive therapy. In contrast, CMV resistance was identified within 2 weeks of therapy for the first episode of CMV viremia in only 2 patients. One patient had a canonical UL97 mutation conferring high level GCV resistance and the other patient had a UL54 mutation conferring low level resistance to GCV and CDV. Both patients responded well to treatment with FOS and had robust ALCs, CD4⁺ and CD8⁺ counts by 6 months from HCT. GCV resistance due to CMV infection with a resistant virus was first reported in 1989. In addition, GCV resistance may arise due to infection first by a susceptible strain and later by a genetically distinct, resistant strain.²¹ While CMV infection with a resistant strain is uncommon,

resistance in the setting of prolonged exposure to GCV and persistent CMV replication was reported in 38% of patients with acquired immunodeficiency syndrome and CMV retinitis that continued to excrete CMV after 3 months of GCV.²²

Two-thirds of patients with resistant CMV had UL97 mutations at nucleotides 594 and 595, which have been associated with high resistance to GCV.²³ The remaining patients had UL54 and/or UL97 mutations conferring resistance to 2 or 3 antivirals. Patients with UL54 mutations had received more extensive exposure to FOS than patients with mutations in UL97 only. The mutations identified in our cohort are in agreement with those recently reported from a commercial reference laboratory in the US.²⁴ Currently available assays for CMV resistance may not identify subpopulations of resistant CMV strains comprising <20% of total resistant CMV strains.⁴ Nine of the 28 (32%) patients with negative CMV resistance testing eventually developed CMV end-organ disease, highlighting challenges in the management of persistent CMV viremia. Patients with late CMV resistance had poor immune reconstitution at 6 months from transplant, as shown by markedly decreased ALC, CD4⁺ and CD8⁺ lymphocyte counts. Lymphopenia is an independent predictor for decreased 1 year survival after T-cell depleted HCT.²⁵ CMV-related mortality at 1 year among patients with CMV resistance was 42%.

The 2 cases in figure 2 present distinct challenges in the management of patients with refractory CMV. In case #10, CMV encephalitis developed despite resolution of CMV viremia with MBV due to lack of MBV penetration into the cerebrospinal fluid.²⁶ CMV from the cerebrospinal fluid was not sent for resistance testing. In case 18, gastrointestinal toxicity due to oral BCV was managed with drug interruptions with eventual emergence of resistant CMV and CMV pneumonitis.

Our study has several limitations inherent to its observational nature. First, we may have underestimated the incidence of CMV resistance as only patients with clinically suspected resistance were tested. We included only probable or definite cases of CMV end-organ disease, thus we may have underestimated the incidence of CMV disease in patients who had contraindications for invasive procedures. In addition, there was substantial heterogeneity in types and dosing of antivirals and other treatment modalities used as preemptive therapy. While acknowledging these limitations, our study provides real world data on CMV for a large, contemporary cohort of CD34⁺ selected HCT using the Food and Drug Administration approved method for CD34⁺ selection. The currently ongoing BMT CTN trial, Progress II, is using the same method for CD34⁺ selection.²⁷

Therapeutic options are currently limited for patients with resistant or refractory CMV. Maribavir (MBV), a CMV specific antiviral is active for CMV strains resistant to GCV and FOS.^{28,29} In a phase 2 study of MBV at doses 400-1200mg twice daily, 67% of patients with resistant or refractory CMV achieved undetectable VLs by week 6; however, recurrence of CMV viremia occurred in approximately 30% of responders.³⁰ Recurrence was most frequently seen among patients with a high VL at baseline which is a particular concern for CD34⁺ selected recipients. MBV has poor penetration into the central nervous system.²⁶ The development of CMV encephalitis in the setting of declining VLs in our patients treated with MBV underscores the need for continued vigilance for central nervous system symptoms

during treatment with MBV. MBV is also in development for preemptive therapy.³¹ Given the lack of myelotoxicity, early and prolonged preemptive therapy with MBV seems feasible and could potentially minimize breakthrough resistance observed after dose interruptions and adjustments with current antivirals.

CMV prevention is an attractive approach to minimize emergence of resistance. Recipients of CD34⁺ selected or haploidentical grafts may optimal candidates for CMV prevention given the high rates of CMV viremia, CMV resistance and the necessity for prolonged antiviral therapy to suppress CMV replication. Letermovir (LTV), a CMV DNA terminase complex inhibitor was recently approved for CMV prophylaxis in adult CMV R⁺ HCT recipients.³² In a phase 3 trial, LTV was effective in preventing CMV viremia or end-organ disease through day +100 after HCT. Compared to placebo, patients on LTV had a survival advantage at 6 months after HCT, notably only 4% of patients on the trial received CD34⁺ selected HCT.^{33–35} Extending CMV prevention beyond day +100 merits further study in CD34⁺ selected HCT recipients specifically given delayed immune reconstitution to CMV and the requirement for prolonged maintenance therapy. Adoptive cell therapy to restore CMV immunity is also an attractive strategy in CD34⁺ selected HCT and randomized clinical trials are needed to formally evaluate this promising modality. CD34⁺ selected HCT recipients are ideally suited for adoptive cell therapy as they do not require pharmacologic immunosuppression and have low rates of acute graft versus host disease.³⁶

In summary, CMV resistance developed in 9% of CMV R⁺, CD34⁺ HCT at 1 year post HCT. The high mortality of patients with resistant CMV highlights the need for new and effective management strategies. MBV is currently in late stages of development for resistant and refractory CMV. LTV recently approved for CMV prophylaxis, is an appealing strategy for recipients of CD34⁺ allografts and merit further dedicated studies. Cellular therapies in development may improve the tempo of immune reconstitution and mortality related to viral infections after CD34⁺ HCT.

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Figure 1.
Plasma CMV PCR by weeks of antiviral treatment

Figure 2a. CMV kinetics of a patient with confirmed UL97 mutation (patient #10)

Description: A 64 year old male with IgA kappa multiple myeloma, s/p autologous transplant x2, received CD34⁺ selected HCT from mismatched unrelated donor, after conditioning with busulfan, melphalan, fludarabine and rabbit antithymocyte globulin. The patient's CMV serology was positive and donor's CMV serology was negative. CMV viremia was treated with GCV induction, then maintenance. On day +152, breakthrough CMV viremia occurred on GCV maintenance. The CMV VL was 11,208 IU/mL and CMV sequencing showed the UL97 mutation (A594V). The patient received FOS and CMV CTLs. On day +221, CMV VL rose to 188,574 IU/mL. On day +224 the patient was enrolled in the MBV phase 2 study with good virologic response. On day +251, the patient was admitted to hospital due to altered mental status. CMV VL in the plasma and cerebrospinal fluid was 553 IU/mL and 16,400 IU/mL respectively. CMV sequencing from the plasma showed the UL97 mutation (A594V). CMV from the cerebrospinal fluid was not sent for resistance testing. The UL54 target could not be amplified likely due to a polymorphism within the primer binding site of one of the PCR products. Abbreviations: CMV, cytomegalovirus; GCV, valganciclovir or ganciclovir; VL, viral load; FOS, foscarnet; MBV, maribavir; HCT, hematopoietic stem cell transplantation

b:

Figure 2b. CMV kinetics of a patient with confirmed UL54 mutation (patient #18)

Description: A 65 year old female with myelodysplastic syndrome received CD34⁺ HCT from mismatched unrelated donor after conditioning with busulfan, melphalan, fludarabine and rabbit antithymocyte globulin. The patient and donor were both CMV seropositive. On day +21, GCV was started for CMV viremia. Later, it was switched to FOS due to cytopenia. On day +80, CMV VL started to increase on maintenance FOS. ADV VL was noted to rise as well. On day +90, BCV (CMX001) was started for ADV viremia with good response. The patient required several interruptions of BCV for management of diarrhea in the next few weeks. GCV was added to BCV with control of CMV. On day +150, CMV started to rise again. On day +164, CMV VL was 3,000 IU/mL. The patient had new oxygen requirements and an abnormal chest X-ray. On day +170, CMV resistance test showed a mixed population (Wild type and N408K). On day +93, only N408K was detected.

Abbreviations: CMV cytomegalovirus; VL, viral load; ADV, adenovirus; GCV, valganciclovir or ganciclovir; FOS, foscarnet; CDV, cidofovir; BCV, brincidofovir; HCT Hematopoietic stem cell transplantation

Table 1

Baseline characteristics of the cohort

Characteristics	CMV R+ HCT recipients	
	n = 220	Percent (100%)
Age, median (range) years	56.8 (19.6-73.3)	
Sex		
Female	118	(53.6%)
Male	102	(46.4%)
CMV serostatus Recipient (R)/Donor (D)		
R+/D+	132	(60.0%)
R+/D-	88	(40.0%)
Donor Type		
Matched related	77	(35.0%)
Matched unrelated	100	(45.5%)
Mismatched unrelated	42	(19.1%)
Mismatched related	1	(0.5%)
Underlying Disease		
Acute leukemia (AL)	107	(48.6%)
Chronic leukemia (CL)	10	(4.5%)
Myelodysplastic syndrome (MDS)	41	(18.6%)
Multiple myeloma (MM)	47	(21.4%)
Other *	15	(6.8%)
Conditioning		
Myeloablative	199	(90.5%)
Reduced intensity	21	(9.5%)

* Non-Malignant hematologic disorder, myeloproliferative disorder

Table 2

Virologic characteristics of patients with and without CMV resistance mutations, among the 47 patients who had resistance testing

		Mutation detected n = 19 (100%)	No mutation detected n = 28 (100%)
Mutation, n (%)			
	UL97 Only	12 (63%)	
	UL97 + UL54	4 (21%)	
	UL54 Only	3 (16%)	
Antiviral resistance, n (%)			
	GCV Only	12 (63%)	
	GCV + FOS	3 (16%)	
	GCV + CDV	3 (16%)	
	GCV + FOS + CDV	1 (5%)	
Days from onset of CMV viremia to detection of mutation, median (IQR)		126 (79-159)	
Days of CMV viremia, median (IQR)		140 (76.5-156)	44 (28-152)
Days of CMV treatment, median (IQR)		114 (72-140)	60 (36.3-95)
Maximum CMV VL log ₁₀ IU/mL, median (IQR)		4.5 (4.1-5.3)	4.1 (3.8-4.6)
CMV VL < 1,000 IU/mL after 6 weeks of CMV treatment, n (%) ⁺		18 (95%)	10 (36%)
Number of weeks with CMV VL [*] > 5000 IU/mL, median (IQR) ⁺		6 (3.5-9.5)	2.5 (1-4)
CMV end-organ disease, n (%)		11 (58%)	9 (32%)
Diagnosis of CMV end-organ disease Days from HCT, median (IQR)		140 (132-186)	170 (98-183)

Abbreviations: n, number; GCV, ganciclovir; FOS, foscarnet; CDV, cidofovir; CMV, cytomegalovirus; IQR, interquartile range; VL, viral load; HCT, hematopoietic cell transplant

^{*} Within single treatment episode

⁺ Denotes significant difference between the two groups ($P < 0.001$)

Table 3

Characteristics of patients with confirmed CMV resistance (n=19)

Pt #	Sex	Age, years	Underlying disease	Onset of CMV viremia Days from HCT (D)	Diagnosis of CMV resistance D	CMV Antivirals (GCV/FOS/CD V) prior to Dx of resistance (days)	Additional CMV treatment after Dx of resistance *	Resistance Mutation ⁺	Resistance to antivirals ⁺	CMV end-organ disease site	CMV end-organ disease Dx D	Survival outcome at 1 year from HCT, D
1	F	61.9	ALL	25	194	167 (93/63/11)	MBV	UL97:A594V	GCV	Colitis; Duodenitis, esophagitis	35; 167	Alive
2	M	22.5	AML	19	34	12 (12/0/0)	FOS; CMV CTL	UL97:L595S	GCV	None	None	Alive
3	F	73.3	AML	28	111	82 (82/0/0)	FOS	UL97:L595F	GCV	None	None	Alive
4	M	36.5	AML	29	205	172 (158/14/0)	None	UL97:L595W	GCV	Retinitis	215	Alive
5	M	57.6	MDS	27	107	74 (74/0/0)	None	UL97:A594P	GCV	None	None	Alive
6	M	65.6	MDS	36	150	114 (114/0/0)	FOS; CMV CTL; BCV	UL97:L595F	GCV	Colitis/Esophagitis	140	Death due to CMV, +295
7	M	63.2	MM	35	84	50 (16/34/0)	None	UL97:C592G	GCV	None	None	Death due to CMV and ADV, +170
8	M	62.6	MM	22	98	70 (70/0/0)	FOS	UL97:L595W	GCV	None	None	Death not related to CMV, +220
9	F	40.9	MM	28	136	106 (103/3/0)	None	UL97:A594V	GCV	Pneumonitis	98	Alive
10	M	64.3	MM	18	152	119 (119/0/0)	FOS; MBV	UL97:A594V	GCV	Encephalitis	256	Death due to CMV, +290
11	M	63.5	MM	29	155	112 (100/12/0)	BCV	UL97:A594V	GCV	Colitis; Encephalitis	142; 279	Death due to CMV, +343
12	F	48.3	MM	29	213	164 (130/34/0)	None	UL97:L595S	GCV	Colitis; Pneumonitis	181; 212	Death due to CMV, +229
13	F	57	ALL	28	187	128 (59/69/0)	None	UL54:F412S UL54:L802M	GCV; FOS CDV	Pneumonitis	134	Death due to viral pneumonia, +221
14	F	67.7	AML	25	91	54 (10/44/0)	CMV CTL	UL97:C603W UL54:L773V ^{\$}	GCV; CDV	None	None	Death not related to CMV, +351
15	M	68.8	AML	26	151	123 (53/70/0)	CMV CTL	UL97:L595F UL54:N495K	GCV; FOS	Colitis	130	Death due to CMV, +329
16	M	69.1	AML	27	183	152 (81/71/0)	None	UL97:A594V UL54:L773V ^{\$}	GCV; FOS	Pneumonitis	191	Death due to CMV, +207
17	M	50.7	AML	25	355	182 (182/0/0)	BCV	UL97:H520Q UL97:T419M UL54:A809V	GCV; FOS	None	None	Alive
18	F	66.5	MDS	33	170	126 (65/61/0)	BCV	UL54:N408K	GCV; CDV	Colitis; Pneumonitis	133; 221	Death due to CMV, +222
19	F	52.5	MM	23	32	10 (3/7/0)	None	UL54:D301N	GCV; CDV	None	None	Alive

Abbreviations: Pt, patient; F, female; M, Male; D, days from HCT; AML: acute myelogenous leukemia, ALL: acute lymphoblastic leukemia; GCV, denotes ganciclovir and/or valganciclovir; FOS, foscarnet; CDV, cidofovir; BCV, brincidofovir (CMX001); MBV, Maribavir; CMV CTL, CMV specific T-lymphocytes; Dx, diagnosis; ADV, adenovirus.

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^{*} Only treatments added after CMV resistance testing are listing. Treatment(s) received prior to resistance testing may have continued after diagnosis of CMV resistance.
[†] Viral phenotypes of the stated mutations are confirmed by marker transfer.^{4,37}
^{\$} L773V conferred resistance to FOS.^{4,38}