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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Does therapeutic drug monitoring (TDM) of trough concentrations suffice for optimizing preemptive therapy with ganciclovir of cytomegalovirus infections in non-renal solid organ transplant recipients?

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Abstract

Objectives: The aim of this study is to explore the relationship between ganciclovir exposure and clinical efficacy and/or safety in non-renal solid organ transplant (SOT) recipients receiving preemptive therapy with ganciclovir/valganciclovir and undergoing therapeutic drug monitoring (TDM)-guided dosing optimization.

Methods: Non-renal SOT recipients admitted to IRCCS Azienda Ospedaliero-Universitaria of Bologna receiving preemptive therapy with ganciclovir or valganciclovir for active cytomegalovirus (CMV) infection and who underwent at least one TDM were included. Desired ganciclovir C_{min} range was set at 1–3 mg/L, and average ganciclovir trough concentrations (C_{min}) were calculated for each patient. Reduced CMV viral load below the lower limit of quantification (LLQ) at 30 days and occurrence of myelotoxicity were selected as the primary outcome. Univariate analysis was performed by comparing patients with average C_{min} below or above 1 or 3 mg/L. Receiver operating characteristic (ROC) curve analysis was performed to identify the average ganciclovir C_{min} cut-off predictive for clinical efficacy or toxicity.

Results: Twenty-nine out of 89 retrieved patients met the inclusion criteria, with a median (interquartile [IQR]) baseline CMV viral load of 27,163 copies/mL (IQR 13 159.75–151 340.25 copies/mL). Reduced CMV viral load below the LLQ at 30 days

Abbreviations: ARC, augmented renal clearance; AUC, area under the curve; BAL, bronchoalveolar lavage; CL_{CR}, creatinine clearance; C_{min}, trough concentration; CMV, cytomegalovirus; CRRT, continuous renal replacement therapy; ECPA, expert clinical pharmacological advice; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; IQR, interquartile range; IV, intravenuos; LLQ, lower limit of quantification; MD, doctor of medicine; PCR, polymerase chain reaction; ROC, receiver operating characteristic; SOT, solid organ transplant; TDM, therapeutic drug monitoring; UHPLC-MS/MS, Ultra-high performance liquid chromatography coupled to tandem mass spectrometry; WHO, World Health Organization.

was found in 17 patients (58.6%). No difference was found in the primary outcome between patients showing average C_{min} below or above 1 mg/L (100.0% vs. 53.8%; $p = .25$) and/or 3 mg/L (65.2% vs. 33.3%; $p = .20$). ROC analysis did not allow to identify an average C_{min} cut-off predictive of clinical efficacy or toxicity.

Conclusions: No clear relationship between ganciclovir C_{min} and neither CMV eradication nor safety issues was identified.

KEYWORDS

ganciclovir, leukopenia, preemptive therapy, solid organ transplant recipients, therapeutic drug monitoring, valganciclovir

1 | INTRODUCTION

Cytomegalovirus (CMV) infection is responsible for remarkable morbidity and mortality among solid organ transplant (SOT) recipients,[1,2] making necessary the treatment of CMV reactivation in high-risk SOT for avoiding severe complications.[3,4]

Ganciclovir and its oral pro-drug valganciclovir are the main-stay agents for managing CMV reactivation or infection.[5] In the last years, great efforts have been implemented for seeking which strategy could be the best for preventing severe CMV infections in SOT recipients. Universal prophylaxis has been the standard approach for several years, but recently preemptive therapy, namely, implementation of antiviral treatment only after positive viremia detection, emerged as an effective strategy in high-risk SOT recipients.[1] Advantages of preemptive therapy versus universal prophylaxis may be reduced occurrence of late-onset CMV infection and minor both drug-related toxicity risk and drug acquisition costs.[6]

Therapeutic use of ganciclovir/valganciclovir is quite challenging as it may be burdened on the one hand by the risk of dose-dependent myelotoxicity and on the other hand by that of CMV breakthrough resistance. Consequently, considering that in preclinical models ganciclovir concentrations ranging from 0.13 to 1.6 mg/L were shown to allow halving CMV replication,[7–9] therapeutic drug monitoring (TDM) has been proposed as a useful tool for optimizing preemptive therapy with ganciclovir.[10]

Unfortunately, some recent real-world clinical studies assessing the role of TDM showed no clear relationships between drug exposure and clinical efficacy or safety.[11–13] Indeed, it could be argued that the conclusions of these studies could have been biased by some confounding factors. The study population was mixed, by including both SOT and hematopoietic stem cell transplant (HSCT) recipients, and ganciclovir/valganciclovir was used either for prophylactic or for therapeutic purposes.[11–13] Besides, a recent position paper about the role of antimicrobial TDM in critically ill adult patients stated that currently no clear evidence exists for defining specific TDM target thresholds of ganciclovir.[14]

The aim of this study was to explore the relationship between ganciclovir exposure and clinical efficacy and/or safety in a homogeneous cohort of SOT recipients receiving preemptive therapy with ganciclovir/valganciclovir and undergoing TDM-guided dosing optimization.

2 | METHODS

All adult non-renal SOT recipients (viz., liver, lung, or heart recipients) hospitalized and/or followed closely as outpatients at the IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, from March 2021 to August 2022 who were treated with preemptive ganciclovir or valganciclovir therapy for active CMV infection and who underwent at least one TDM were retrospectively included. Kidney transplant recipients were excluded because they received a universal prophylaxis strategy. CMV infection or disease was defined according to clinical and viral load criteria.[4,6,15] Specifically, in regard to clinically suspected invasive pulmonary disease, proven CMV pneumonia requires clinical and/or radiological symptoms and/or signs of pneumonia coupled with CMV documented in lung tissue, whereas probable CMV pneumonia is defined as the detection of CMV in bronchoalveolar lavage (BAL) fluid coupled with clinical and/or radiological symptoms and/or signs of pneumonia. Patients who received ganciclovir/valganciclovir prophylaxis were excluded. The study was reviewed and approved by the Ethics Committee of Azienda Ospedaliero-Universitaria of Bologna (No. EM887-2022_326/2021/Oss/AOUBo).

Demographic (age, sex, weight, height, body mass index) and clinical/laboratory data (type of SOT, intensive care unit [ICU] admission, creatinine clearance (CL_{CR}), need for continuous renal replacement therapy [CRRT] or intermittent hemodialysis, occurrence of augmented renal clearance (ARC), white blood cells count, hemoglobin, platelet count, absolute number of neutrophils at baseline) were retrieved for each patient. ARC was defined as a measured $CL_{CR} \geq 130$ mL/min/1.73m^2 in males and ≥ 120 mL/min/1.73m^2 in females coupled with a normal serum creatinine value.[16] Ganciclovir or valganciclovir dosage, time from transplant to initiation of antiviral therapy, number of TDM assessments per patient, time to first TDM assessment, and number of ganciclovir/valganciclovir dosing adjustments were also collected. Data on blood CMV-DNA load at baseline and throughout antiviral treatment were retrieved. CMV-DNA assay was performed on whole blood samples by using a commercial quantitative real-time polymerase chain reaction as previously described.[17] The analytical sensitivity of the assay was 10 copies of target DNA per amplification reaction. The lower limit of quantification (LLQ) of the assay was 300 copies/mL whole blood.

Ganciclovir or valganciclovir was prescribed at the discretion of the attending physician or infectious disease consultant in terms of dosage and duration according to current guidelines[4] and clinical practice implemented at our University hospital for each type of SOT. Briefly, two different scenarios of preemptive therapy were adopted depending on the CMV serum status: (a) always in CMV seropositive (D+/R+ or D?/R+) liver-, lung-, or heart-transplant recipients; (b) in high-risk CMV seronegative (D+/R- or D?/R-) liver-, heart-, or lung-transplant recipients whenever, after completing an initial period of ganciclovir/valganciclovir prophylaxis (3 months in liver- and heart-, and 6–12 months in lung-transplant recipients), a blood CMV-DNA viral load ≥ 10 000 copies/mL was detected. CMV-DNA viral load was screened weekly by means of whole-blood quantitative polymerase chain reaction. Preemptive therapy was started with an induction regimen of intravenuos ganciclovir 5 mg/kg q12h or oral valganciclovir 900 mg q12h eventually adjusted to renal function. Blood samples for measuring serum ganciclovir trough concentrations (C_{min}) were collected 5–15 min before one of the daily administrations after achieving steady-state conditions (viz., at least four prior doses of ganciclovir or valganciclovir). Total serum concentrations of ganciclovir were measured by means of a validated ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS) method.[18] Precision and accuracy were assessed by replicate analysis of quality control samples against calibration standards. The intra- and interassay coefficients of variation were always < 10%. The LLQ was 0.1 mg/L. The TDM results were made available, usually within 4–6 h, via the intranet to doctor of medicine clinical pharmacologists who performed an individualized expert clinical pharmacological advice (ECPA) for dosing optimization in each single patient within the same day as previously described.[19,20] Desired range of ganciclovir C_{min} was set at 1.0–3.0 mg/L according to recent findings,[11] and dosing adjustments were recommended whenever values were outside of this range.

The primary outcome of clinical efficacy was reduction of CMV viral load below the LLQ at 30 days. Secondary outcomes included time to negativity, rate of persistent infection (defined as a drop of CMV viral load < 1-log after 2 weeks of treatment), the occurrence of resistance development with treatment escalation to foscarnet or other antivirals, and mortality rate during ganciclovir/valganciclovir treatment course. The primary outcome of toxicity was the occurrence of leukopenia, neutropenia, thrombocytopenia, or anemia at any time during treatment. Furthermore, the occurrence of hepatotoxicity and neurotoxicity during ganciclovir/valganciclovir was also assessed. Hematologic parameters were defined according to the Common Terminology Criteria for Adverse Events: leukopenia as a white blood cell count < 3.5×10^9/L or a decrease ≥ 20%, compared to the baseline value; neutropenia as an absolute neutrophil count < 1.0×10^9/L or administration of granulocyte colony-stimulating factor; thrombocytopenia as a platelet count < 100×10^9/L, a decrease ≥ 50%, compared to the baseline value, or the need for platelet administration; and anemia as a hemoglobin concentration of < 8.0 g/dL, a decrease ≥ 20%, compared to the baseline value, or the need for red blood cell transfusion.[21] Hepatotoxicity was defined as an increase up to twice the upper limit of normal for serum alanine aminotransferase or aspartate aminotransferase. Neurotoxicity was defined and assessed by subjective descriptions reported in electronic medical records.

Descriptive statistics were used to describe the patient sample, with continuous data presented as the median and interquartile range (IQR), whereas categorical variables were expressed as count and percentage. Univariate analyses were performed by using the Fisher exact test, χ^2 test, or Mann–Whitney U test as appropriate. The receiver operating characteristic (ROC) curve analysis was performed by selecting ganciclovir average C_{min} as the test variable and the different efficacy/toxicity outcomes as the state variable, and area under the curve (AUC) along with 95% confidence interval (CI) were calculated. The optimal cut-off point was computed using the Youden Index method. Youden Index was calculated according to the following equation: sensitivity (%) + specificity (%) − 100. Linear correlation between ganciclovir average C_{min} and time to CMV negativity was also calculated. A p-value < .05 was considered significant. Statistical analysis was performed using MedCalc for Windows (MedCalc statistical software, version 19.6.1, MedCalc Software Ltd.).

3 | RESULTS

Among a total of 89 patients who underwent TDM-guided ganciclovir/valganciclovir therapy in the period March 2021–August 2022, 29 fulfilled the inclusion criteria and were selected (Figure 1). Demographics and clinical characteristics of the included patients are reported in Table 1.

The median age was 56 years (IQR 50–63 years), with male preponderance (86.2%). The median CL_{CR} at baseline was 50.5 mL/min/1.73m^2 (IQR 27.0–94.25 mL/min/1.73m^2), and four patients (13.8%) had ARC. ICU admission was required in 10 cases (34.5%), and five patients underwent CRRT. Non-renal SOT patients were lung-, liver-, and heart-transplant recipients in 15, nine, and five cases, respectively. Seven out of the 29 included SOT recipients were CMV seronegative (24.2%), being a donor/recipient mismatch documented in four cases.

CMV viral load ≥ 10 000 copies/mL was detected in 28/29 patients, with a median baseline CMV viral load on whole blood of 27 163 copies/mL (IQR 13 159.75–151 340.25 copies/mL). Pulmonary CMV reactivation was documented in 17 out of 29 cases, with a median baseline CMV viral load on BAL of 267 820 copies/mL (IQR 78 675–813 647 copies/mL). Seven out of the 17 pulmonary CMV reactivation were defined as proven or probable CMV pneumonia (in five cases, ICU admission and mechanical ventilation were required). In two cases, a multiorgan invasive CMV disease was documented with biopsy-proven gastrointestinal and bronchial involvement. Antiviral therapy was started after a median of 50 days (IQR 33–112 days) from SOT.

A total of 178 TDM-guided ECPAs were performed, with a median number of 4 (IQR 3–6) per patient. Overall, ganciclovir/valganciclovir dosing adjustments were recommended in 56 out of 178 ECPAs (31.5%, with 9.6% increases and 21.9% decreases). The initial

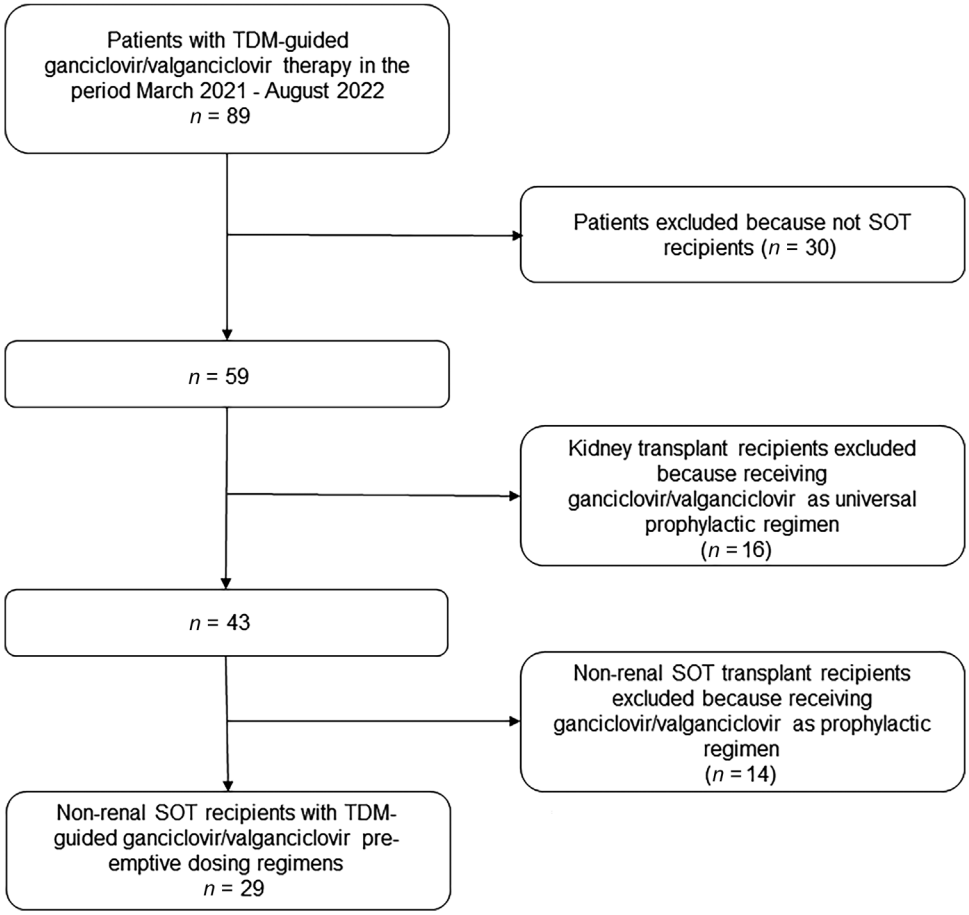

FIGURE 1 Flowchart of patient inclusion and exclusion criteria. SOT, solid organ transplant; TDM, therapeutic drug monitoring.

ganciclovir/valganciclovir dosing regimens were adjusted at the first TDM assessment in 15 out of 29 patients (51.7%, with 34.5% decreases and 17.2% increases).

Outcomes in terms of clinical efficacy and safety were reported in Table 2. Reduction of CMV viral load below the LLQ at 30 days was shown in 17/29 patients (58.6%), after a median time of 20.5 days (IQR 14.5–27.5 days). No significant correlation emerged between ganciclovir average C_{min} and time to CMV negativity ($r = .26$; $p = .25$). Persistent infection occurred in eight patients (27.6%). In three cases (10.3%; two lung- and one heart-transplant recipients), breakthrough resistance to ganciclovir occurred (Table 3). A trend to a higher risk of ganciclovir underexposure at first TDM was found in patients developing resistance (66.7% vs. 15.4%; $p = .09$). Two patients (6.9%) died during the antiviral treatment course for causes unrelated to the CMV infection. Regarding safety outcomes, 21/29 patients (72.4%) developed leukopenia, and neutropenia was reported in 7/29 cases (24.1%). Ganciclovir was discontinued in four out of the 21 patients in which leukopenia occurred, whereas in no case granulocyte colony-stimulating factor was used. Thrombocytopenia and anemia were found in three (10.3%) and six (20.7%) patients, respectively. Concomitant agents causing myelotoxicity were used in 20 out of 29 patients (69.0%), being cotrimoxazole plus mycophenolate the most frequent (44.8%). Five patients (17.2%) developed hepatotoxicity during ganciclovir/valganciclovir treatment, whereas no case of neurotoxicity occurred.

ROC analysis did not allow to identify an average C_{min} cut-off predictive either of clinical efficacy or of toxicity (Supplementary Table S1). Overall, three out of 29 patients (10.3%) had an average C_{min} below 1 mg/L and showed a trend toward a lower rate of leukopenia, compared with those having an average $C_{min} > 1$ mg/L (0.0% vs. 65.4%; $p = .06$; Supplementary Table S2). No other difference in terms of clinical efficacy and/or safety outcomes emerged (Supplementary Table S2). A total of six out of 29 patients (20.7%) had an average $C_{min} > 3$ mg/L, and no difference emerged in terms of clinical efficacy and/or safety outcomes, compared with those having an average $C_{min} < 3$ mg/L (Supplementary Table S3).

Univariate analysis comparing patients with a reduction of CMV viral load below the LLQ versus those with detectable viral load at 30 days is summarized in Table 4. No significant differences emerged between the two groups. A higher proportion of liver transplant recipients (77.8%) showed a reduction of CMV viral load below the LLQ at 30 days, compared to lung- (53.3%) or heart-transplant recipients (40.0%), although not statistically significant.

The occurrence of leukopenia was 100.0%, 86.7%, and 33.3% in heart-, lung-, and liver-transplant recipients, respectively. A lower leukopenia occurrence was reported among liver transplant

TABLE 1 Demographics and clinical variables of non-renal solid organ transplant (SOT) recipients treated with ganciclovir/valganciclovir non-prophylactic dosing regimen.

Patient demographic	Patients ($N = 29$)
Age (years; median [IQR])	56 (50–63)
Gender (male/female; *n* [%])	25/4 (86.2/13.8)
Body weight (kg; median [IQR])	74 (60–88)
Body mass index (kg/m^2; median [IQR])	24.4 (22.0–28.4)
Serum creatinine (median [IQR]; mg/dL)	1.29 (0.80–2.15)
Estimated CL_{CR} (mL/min/1.73 m^2; median [IQR])	50.5 (27.0–94.25)
ICU admission (*n* [%])	10 (34.5)
Continuous renal replacement therapy (CRRT; *n* [%])	5 (17.2)
Augmented renal clearance (ARC; *n* [%])	4 (13.8)
SOT (*n* [%])	
Lung	15 (51.7)
Liver	9 (31.1)
Heart	5 (17.2)
Donor/recipient status (*n* [%])	
D+ / R+	7 (24.1)
D+ / R−	4 (13.8)
D? / R+	15 (51.7)
D? / R−	3 (10.4)
CMV (*n* [%])	
Viremia	28 (96.6)
BAL CMV replication	17 (58.6)
Proven or probable CMV pneumonia	7 (24.1)
Biopsy-proven invasive disease	2 (6.9)
Baseline CMV viral load (copies/mL; median [IQR])	27 163 (13 159.75–151 340.25)
Baseline CMV viral load (IU; median [IQR])	12 495 (6053.5–69 616.5)
Baseline CMV viral load on BAL (copies/mL; median [IQR])	267 820 (78 675–813 647)
Baseline CMV viral load on BAL (IU; median [IQR])	123 197 (36 191–374 278)
Baseline laboratory data	
White blood cell count (10^9/L; median [IQR])	5.74 (3.83–9.60)
Leukopenia (*n* [%])	3 (10.4)
Absolute neutrophil count (10^9/L; median [IQR])	4.26 (2.93–6.47)
Neutropenia (*n* [%])	1 (3.4)
Platelet count (10^9/L; median [IQR])	146 (97–185)
Thrombocytopenia (*n* [%])	9 (31.0)
Hemoglobin (median [IQR]; g/L)	10.0 (8.7–10.5)
Anemia (*n* [%])	0 (0.0)
Concomitant agents causing myelotoxicity	
Overall (*n* [%])	20 (69.0)
Cotrimoxazole + mycophenolate (*n* [%])	13 (44.8)
Cotrimoxazole (*n* [%])	5 (17.2)
Linezolid (*n* [%])	1 (3.5)
Azathioprine (*n* [%])	1 (3.5)
Ganciclovir/valganciclovir treatment	
No. of TDM assessments per patient (median [IQR])	4 (3–6)
C_{min} average (median [IQR])	1.83 (1.43–2.66)
Time to start treatment after SOT (days; median [IQR])	50 (33–112)
Median time to first TDM (days; median [IQR])	4 (3–6)
Expert clinical pharmacological advice (ECPA; *n* [%])	
Overall ECPAs	178
No. of dosages confirmed	122 (68.5)
No. of dosages decrease	39 (21.9)
No. of dosages increase	17 (9.6)
First TDM assessment in therapeutic range	14 (48.3)
First TDM decrease	10 (34.5)
First TDM increase	5 (17.2)

Abbreviations: BAL, bronchoalveolar lavage; CL_{CR}, creatinine clearance; C_{min}, trough concentration; CMV, cytomegalovirus; ICU, intensive care unit; IQR, interquartile range; IU, international unit; TDM, therapeutic drug monitoring.

recipients, compared to heart- or lung-transplant recipients ($p = .006$; Supplementary Table S4). No other significant differences emerged between patients with leukopenia occurrence, compared to those with no decrease in white blood cell count.

4 | DISCUSSION

Our study explored the role of a TDM-guided strategy in optimizing ganciclovir/valganciclovir preemptive therapy in a cohort of non-renal SOT recipients. Our findings suggested that standard dosing regimens of ganciclovir/valganciclovir adjusted for renal function allowed the attainment of the desired trough level at first TDM assessment in approximatively half of the patients and that the need for further dosing adjustments concerned more than 30% of ECPAs during the overall treatment. These findings are consistent with those reported in previous recent real-world studies conducted in similar scenarios.[11,12] Ritchie et al.[11] found that ganciclovir C_{min} was within the desired range of 1–3 mg/L in 55.2% of cases among a heterogeneous cohort of

TABLE 2 Clinical efficacy and safety outcomes of SOT recipients receiving ganciclovir/valganciclovir non-prophylactic dosing regimens.

Variable	Patients ($N = 29$)
Efficacy	
Reduction of CMV viral load below the lower limit of quantification at 30 days	17 (58.6)
Median time to negativization (IQR)	20.5 (14.5–27.5)
Detectable viral load at 30 days	11 (37.9)
Persistent infection	8 (27.6)
Mortality during treatment course	2 (6.9)
Resistance development and escalation to foscarnet or anti-CMV immunoglobulin	3 (10.3)
Safety	
Overall leukopenia	21 (72.4)
White blood cell count < $3.5*10^9$/L	17 (58.6)
White blood cell count 20% decrease from baseline	18 (62.1)
Neutropenia	7 (24.1)
Overall thrombocytopenia	3 (10.3)
Platelet count < $100*10^9$/L	3 (10.3)
Platelet count 50% decrease from baseline	2 (6.9)
Overall anemia	6 (20.7)
Hemoglobin < 8.0 g/dL	6 (20.7)
Hemoglobin 20% decrease from baseline	1 (3.4)
Hepatotoxicity	5 (17.2)
Neurotoxicity	0 (0.0)

Abbreviations: CMV, cytomegalovirus; IQR, interquartile range.

CMV-infected patients having hematological or autoimmune disorders, HIV infection, or being SOT recipients. Similarly, Martson et al.[12] reported that dosing adjustments were needed in 29% cases of SOT and HSCT recipients receiving ganciclovir or valganciclovir as prophylaxis or treatment.

Unfortunately, ROC analysis did not show any clear relationship between ganciclovir C_{min} and clinical response in terms of undetectable CMV viral load at 30 days. Overall, our findings are consistent with those coming from previous real-world studies, which did not find any clear relationship between ganciclovir C_{min} and CMV eradication.[11–13] Several reasons could explain why measuring C_{min} could not be enough for this purpose. First, preclinical studies showed that the IC_{50} needed for reducing CMV replication by 50% was quite variable, ranging from 0.1 to 1.7 mg/L.[7,8,22,23] The IC_{90} needed for reducing CMV replication by 90% could be a more clinically relevant concentration as it reflects what is aimed during treatment. However, the IC_{90} was found to be as high as 3.5 mg/L,[24] namely, a value higher than the C_{min} upper safety threshold that is currently applied in clinical practice for avoiding dose-dependent toxicity risk. Indeed, recent studies showed that the 24-h area under the concentration time curve (AUC_{24h}) could be a better predictor of clinical outcome. A target AUC_{24h} of 40–50 mg•h/L was associated with decreased risk of CMV infection for adults undergoing CMV prophylaxis,[25] whereas that of 80–120 mg•h/L was suggested for granting efficacy in the treatment of active CMV disease.[26] Unfortunately, previous studies showed that C_{min} was quite poorly correlated with the AUC_{24h},[12,25] and this furtherly strengthens the hypothesis that C_{min} per se could not be a valuable predictor of CMV viral load decrease.

Dose-dependent ganciclovir/valganciclovir-related leukopenia occurred in more than two-thirds of SOT recipients included in our study. This is in agreement with previous real-world studies reporting a prevalence of leukopenia ranging from 36% to 96% during ganciclovir prophylaxis and/or treatment.[11–13] Unfortunately, ROC analysis did not allow to identify a threshold of ganciclovir C_{min} helpful in predicting the likelihood of this adverse event. We found a trend toward lower leukopenia occurrence among patients having average $C_{min} < 1$ mg/L, compared with those having $C_{min} \geq 1$ mg/L, but this disappeared when comparing average $C_{min} > 3$ mg/L versus ≤ 3 mg/L. Available data in the literature are inconsistent with respect to such safety issues. Ritchie et al. did not find any significant association between leukopenia occurrence and serum ganciclovir peak and trough concentrations.[11] Martson et al. found at multivariate analysis a significant relationship between the highest C_{min} and AUC_{24h} values and the decrease in white blood cells count.[12] A retrospective analysis found a significant correlation between ganciclovir C_{min} and lymphopenia but not leukopenia among 46 SOT recipients.[13] Indeed, it should also be mentioned that the remarkable proportion of leukopenia occurring among SOT patients may recognize several multifactorial causes other than ganciclovir/valganciclovir treatment, namely, therapy with immunosuppressants or with cotrimoxazole or the co-presence of other underlying diseases.[27] Indeed, more than two-thirds of our patients received myelotoxic agents during ganciclovir/valganciclovir treatment, thus their role in contributing to the relevant proportion of leukopenia occurrence cannot be ruled out.

Although according to both our and previous findings the role of ganciclovir TDM could be questionable, as also stated in a recent position paper,[14] further studies investigating the relationship between ganciclovir/valganciclovir exposure (in terms of both C_{min} and AUC_{24h}) and efficacy and/or safety will be required for definitively assessing the clinical usefulness of a TDM-guided approach.

It is noteworthy that novel antiviral agents (i.e., letermovir, maribavir) have been recently issued in order to overcome resistance and toxicity occurrence reported with ganciclovir and/or foscarnet.[28] Although real-world evidence is still limited, preliminary evidence found a significantly lower rate of myelotoxicity and nephrotoxicity with the use of letermovir and/or maribavir, compared to traditional antiviral agents.[29,30]

We are aware of some limitations of our study. The retrospective study design and the limited sample size should be acknowledged. Furthermore, CMV-DNA viral load was not reported in IU/mL as recommended by World Health Organization international guidelines.[6] Conversely, a strength element is represented by the fact that the analysis was carried out in a homogeneous cohort of patients composed entirely of non-renal SOT recipients.

TABLE 3 Clinical features of patients developing ganciclovir resistance during CMV treatment.

ID case	Age/Sex	Type of SOT	Time from SOT to CMV reactivation	Immunosuppressive therapy	Lymphocyte count	Average ganciclovir C_{min} (mg/L)	No. of TDM in which ganciclovir $C_{min} < 1$ mg/L	Ganciclovir underexposure at first TDM	Time to ganciclovir resistance occurrence after starting therapy	Type of mutation	Therapeutic strategy	Outcome
#1	43/M	Lung	181	Mycophenolate 500 mg/day Tacrolimus 4.5 mg q12h Prednisone 25 mg/day	1.3×10^9/L	1.26	1/5 (20.0%)	Yes (0.9 mg/L)	35	UL97 gene A594V mutation	Anti-CMV immunoglobulin	Favorable
#2	60/M	Lung	116	Everolimus 0.25 mg/day Tacrolimus 0.5 mg/day Prednisone 25 mg/day	0.32×10^9/L	1.66	6/33 (18.2%)	No (2.2 mg/L)	112	UL97 gene M460I and L595S mutations	Switch to foscarnet	Favorable
#3	36/F	Heart	93	Mycophenolate 1500 mg/day Tacrolimus 4 mg q12h Prednisone 15 mg/day	0.54×10^9/L	1.73	1/6 (16.7%)	Yes (0.4 mg/L)	73	UL 97 gene L595S mutation	Switch to foscarnet	Favorable

Abbreviations: C_{min}, trough concentration; TDM, therapeutic drug monitoring.

TABLE 4 Univariate analysis comparing SOT recipients showing 30-day CMV negativization versus those with no 30-day CMV negativization.

Variable	30-day CMV negativization ($n = 17$)	30-day CMV no negativization ($n = 12$)	*p*-value
Age (years; median [IQR])	59 (50.75–64)	54 (43–61)	.21
Gender (male/female; *n* [%])	14/3 (82.4/17.6)	11/1 (91.7/8.3)	.62
Body weight (kg; median [IQR])	85 (61.5–90)	67.5 (60–80.5)	.19
Body mass index (kg/m^2; median [IQR])	25.7 (23.9–28.6)	22.9 (19.3–26.0)	.08
ICU admission (*n* [%])	7 (41.2)	3 (25.0)	.45
CRRT (*n* [%])	3 (17.6)	2 (16.7)	.99
ARC (*n* [%])	3 (17.6)	1 (8.3)	.62
SOT (*n* [%])			
Lung	8 (47.0)	7 (58.3)	.71
Liver	7 (41.2)	2 (16.7)	.23
Heart	2 (11.8)	3 (25.0)	.62
Donor/recipient status (*n* [%])			
D+ / R+	4 (23.5)	3 (25.0)	.72
D+ / R−	2 (11.8)	2 (16.7)	
D? / R+	10 (58.8)	5 (41.6)	
D? / R−	1 (5.9)	2 (16.7)	
CMV (*n* [%])			
Viremia	17 (100.0)	11 (91.7)	.86
BAL CMV replication	9 (52.9)	8 (66.7)	
Biopsy-proven invasive disease	1 (5.9)	1 (8.3)	
Baseline CMV viral load (copies/mL; median [IQR])	20 902 (12 131–94 249)	41 752 (16 557–931 892)	.12
Baseline CMV viral load on BAL (copies/mL; median [IQR])	301 646 (81 320–1 213 336)	236 015 (50 866–1 010 993)	.89
Ganciclovir/valganciclovir treatment			
Ganciclovir administration	8 (47.0)	7 (58.3)	.83
Valganciclovir administration	5 (29.5)	3 (25.0)	
Ganciclovir followed by valganciclovir	4 (23.5)	2 (16.7)	
Ganciclovir dosing regimen (mg/day; median [IQR])	371.7 (255.2–463.4)	350 (154.7–598.8)	.75
Valganciclovir dosing regimen (mg/day; median [IQR])	956.3 (785.7–1350)	1012.5 (465.4–1800)	.69
No. of TDM assessments per patient (median [IQR])	4 (3–8.5)	4 (1.5–6)	.79
C_{min} average (median [IQR])	1.83 (1.17–2.49)	2.06 (1.54–3.39)	.35
Time to start treatment after SOT (days; median [IQR])	50 (38.25–119.5)	51.5 (32.5–104.5)	.95
Median time to first TDM (days; median [IQR])	4 (3–6.25)	4 (2.5–5.5)	.84
Clinical pharmacological advice (*n* [%])			
No. of dosages confirmed	67 (67.0)	55 (70.5)	.75
No. of dosages increase	11 (11.0)	6 (7.7)	
No. of dosages decrease	22 (22.0)	17 (21.8)	
First TDM assessment in therapeutic range	9 (52.9)	5 (41.7)	.78
First TDM increase	3 (17.6)	2 (16.6)	
First TDM decrease	5 (29.5)	5 (41.7)	

Abbreviations: BAL, bronchoalveolar lavage; C_{min}, trough concentration; CMV, cytomegalovirus; ICU, intensive care unit; IQR, interquartile range; TDM, therapeutic drug monitoring.

In conclusion, our analysis did not find any clear relationship between ganciclovir C_{min} and either CMV eradication or safety issues. Hopefully, prospective studies of real-time TDM-guided ganciclovir dosing optimization, compared to standard approach, including prophylactic scenario, could be helpful in addressing this still unresolved issue.

AUTHOR CONTRIBUTIONS

Conceptualization: Milo Gatti, Matteo Rinaldi, Maddalena Giannella, and Federico Pea. *Methodology*: Milo Gatti and Matteo Rinaldi. *Formal analysis*: Milo Gatti. *Data curation*: Milo Gatti and Matteo Rinaldi. *Writing—original draft preparation*: Milo Gatti and Matteo Rinaldi. *Writing—review and editing*: Luciano Potena, Elena Salvaterra, Maria Cristina Morelli, Maddalena Giannella, Pierluigi Viale, and Federico Pea. *Funding acquisition*: Federico Pea. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Milo Gatti received personal fees from Angelini; Pierluigi Viale has served as a consultant for Biomerieux, Gilead, Merck Sharp and Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher, and Venatorx and received payment for serving on the speaker's bureau for Correvio, Gilead, Merck Sharp and Dohme, Nordic Pharma, and Pfizer; Federico Pea participated in a speaker bureau for Angelini, Basilea Pharmaceutica, Gilead, Hikma, Merck Sharp and Dohme, Nordic Pharma, Pfizer, and Sanofi Aventis and on an advisory board for Angelini, Basilea Pharmaceutica, Correvio, Gilead, Merck Sharp and Dohme, Nordic Pharma, Novartis, Pfizer, and Thermo-Fisher. The authors report no other conflicts of interest in this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria of Bologna (EM887-2022_326/2021/Oss/AOUBo on October 19, 2022). Signed informed consent was waived due to the retrospective and observational nature of the investigation according to hospital agreements.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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