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MATCH
Management of Post-Transplant Infections in Collaborating Hospitals

Impact of CMV PCR Blips in Recipients of Solid Organ and Haematopoietic Stem Cell Transplantation

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INTRODUCTION

Viral blips reflecting PCR artefacts or transient low-level replication are well described in the HIV setting[1-5]. The epidemiology of such blips in transplant recipients screened for CMV with PCR is uncertain, and was investigated in a cohort of solid organ (SOT) and haematopoietic stem cell (HSCT) recipients.

AIM OF THE STUDY

- To study the prevalence and distribution of CMV blips among SOT and HSCT recipients
- Determine the probability of the first positive CMV PCR being a CMV blip
- Investigate if CMV blips can predict subsequent CMV infection

METHODS AND DESIGN

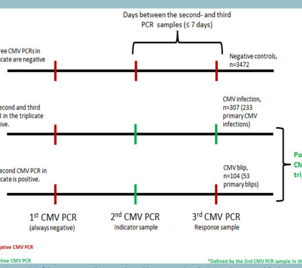
SOT and HSCT recipients transplanted between 2010-2015, who had a known donor (D)/recipient (R) CMV IgG serostatus (D+/R+, D+/R- or D-/R+), and with ≥3 CMV PCRs fulfilling the CMV PCR triplicate criteria (**Figure 1**) were included (N=851). Odds ratio (OR) for factors associated with a triplicate being a blip was estimated using logistic regression. Whether blips affected the hazard ratio (HR) for subsequent CMV infection was determined with a Cox model.

RESULTS

851 transplant recipients generated 3,883 CMV PCR triplicates (104 blips, 307 infections, 3,472 negatives) (**Figure 1 and Table 1**). Of the 307 CMV infection triplicates, 233 were first time infections and the remaining 74 constituted recurrent infection/s. Out of the 104 CMV PCR triplicates representing CMV blips, 53 were first time blips that occurred before CMV infection.

Figure 1

Definition of the CMV PCR triplicate and the different outcomes



The CMV PCR triplicate consist of three consecutive samples, with ≤ seven days between the second (index sample) and the third (response sample) CMV PCRs. There are three different outcomes of this model: **1**. Negative control triplicates, were all three CMV PCRs in the triplicate are negative; **2**. CMV triplicates indicating CMV infection were both the indicator and response sample are positive; **3**. CMV triplicates indicating CMV blips, where the indicator sample being the only positive sample.
The lower limit of quantification of the CMV PCR kit used was 273 IU/mL.

Table 1

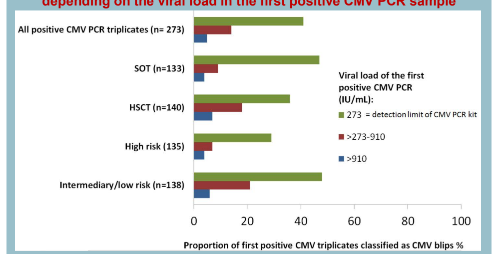
Characteristics of 851 transplant recipients generating a total of 3,883 CMV PCR triplicates

Characteristics	Total N=851	SOT N=476	HSCT N=375	p-value*
Baseline demographics				
Median age (IQR), years	48 (32-59)	49 (37-58)	47 (22-61)	0.05
Male gender (%)	504 (59)	278 (58)	226 (60)	0.6
Risk of CMV infection according to CMV IgG status**				
High risk of CMV infection	276 (32%)	123 (26%)	153 (41%)	<0.0001
Intermediary/low risk of CMV infection	575 (68%)	353 (74%)	222 (59%)	<0.0001
Number of patients with a first CMV infection* (%)**	233 (27 [95%CI 24-30])	114 (24 [95%CI 20-28])	119 (32 [95%CI 27-36])	0.01
CMV PCR triplicates				
Total amount of CMV PCR triplicates	3,883 (100)	1,269 (33 [95%CI 31-34])	2,614 (67 [95%CI 66-69])	<0.0001
Number of negative controls (% of total amount of CMV triplicates)	3,472 (89 [95%CI 88-90])	1,092 (86 [95%CI 84-88])	2,380 (91 [95%CI 90-92])	<0.0001
Number of CMV triplicates representing CMV infection (% of total amount of CMV triplicates)	307 (8 [95%CI 7-9])	140 (11 [95%CI 9-13])	167 (6 [95%CI 5-7])	<0.0001
Number of blips (% of blips out of total amount of CMV triplicates)	104 (3 [95%CI 2-3])	37 (3 [95%CI 2-4])	67 (3 [95%CI 2-3])	0.5

*p-value describes SOT vs HSCT.
** Risk of CMV infection according to donor (D)/recipient (R) CMV IgG serostatus (+/-) at the time of transplantation. For solid organ transplantation recipients D+/R- is associated with high risk of CMV infection, while D-/R+ is associated with low risk. Amongst bone marrow transplant recipients, D-/R+ is associated with a high risk of CMV infection, whereas D+/R- is associated with a low risk. For both types of transplantation, D+/R+ is associated with intermediary risk of CMV infection. Due to the low number of patients in the low risk group, these patients are analysed together with the intermediate group.
*** CMV infection defined as two consecutive CMV PCRs ≥273 IU/mL taken within seven days of each other.
Abbreviations: CI; confidence intervals, CMV; cytomegalovirus, HSCT; haematopoietic stem cell transplantation, IQR; inter quartile range, SOT; solid organ transplantation.

Figure 2

Distribution of CMV blips amongst the first positive CMV PCR triplicates depending on the viral load in the first positive CMV PCR sample



Distribution of CMV blips according to the viral load in the first positive (indicator) CMV PCR and stratified for type of transplantation and donor/recipients CMV IgG serostatus.
For solid organ transplantation recipients D+/R- is associated with high risk of CMV infection, while D-/R+ is associated with low risk. Amongst bone marrow transplant recipients, D-/R+ is associated with a high risk of CMV infection, whereas D+/R- is associated with a low risk. For both types of transplantation, D+/R+ is associated with intermediary risk of CMV infection. Due to the low number of patients in the low risk group, these patients are analysed together with the intermediate group.
*Negative control CMV PCR triplicates are not included in the figure.

The proportion of blips was lower the higher the viral load of the first positive indicator CMV PCR sample of the triplicate, and decreased with increasing viral load (**Figure 2**). This pattern also persisted after stratifying for type of transplantation and risk associated with CMV IgG serostatus (**Figure 2**).
The Odds Ratio (OR) of a triplicate representing a blip decreased with increasing viral load of the second sample ([vs=273 IU/ml]; >273-910 IU/mL: OR 0.2 [95% CI 0.1-0.5], >910 IU/mL: 0.08 [95% CI 0.02-0.2], p ≤0.0002) and increased with intermediary/low risk serostatus (vs high risk) (2.8 [95%CI 1.2-5.5] p=0.01) (Table 2). If the cumulative exposure to viremia in the CMV blips was >910 IU/mL, there was a higher risk of subsequent CMV infection (HR 4.6 [95% CI 1.2-17.2] p=0.02) (**Figure 3**).

CONCLUSIONS

In this study, we demonstrate that CMV blips occur in approximately 19% of the first positive CMV PCR samples obtained while screening transplant recipients with CMV PCR. CMV blips are particularly frequent if the viral load of the first positive PCR (the indicator sample in **Figure 1**) is at the detection limit or if the patient has intermediary/low risk serostatus.
Furthermore, the cumulative viral load of CMV blips influence the risk of CMV infection, suggesting that these blips at least partly reflect low-level viremia rather than merely intermittent false positive results caused by the technology.
Thus, the characteristics of CMV blips are important markers for subsequent infection. Upon detection of a first positive CMV PCR, these observations should be carefully considered by the clinician before initiation of anti-CMV treatment.

Table 2

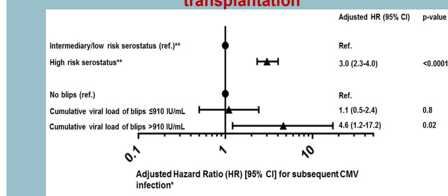
The odds ratio (OR) of the first positive indicator CMV PCR* being a CMV blip

Factors	Univariate			Multivariate**		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
Use of anti-CMV treatment in relation to the CMV PCR triplicate						
No treatment	Ref.			Ref.		
Treatment initiated before the indicator sample	0.2	0.05-1.2	0.06	0.4	0.07-1.8	0.2
Treatment initiated between indicator and response samples	1.1	0.6-2.1	0.6	1.8	0.8-3.7	0.1
Risk associated with CMV IgG serostatus of donor and recipient						
High risk	Ref.			Ref.		
Intermediary/low risk	3.0	1.6-5.8	0.0009	2.8	1.2-5.5	0.01
Viral load of the indicator CMV PCR in the CMV PCR triplicate (IU/mL)						
=273***	Ref.			Ref.		
>273-910	0.2	0.1-0.5	<0.0001	0.2	0.1-0.5	0.0002
>910	0.08	0.03-0.2	<0.0001	0.08	0.02-0.2	<0.0001

The odds ratio (OR) of the first positive indicator CMV PCR being a CMV blip.
*For each patient with a positive CMV PCR triplicate (273 patients), the odds of the first positive CMV PCR/patient being a CMV blip, and not an infection, was modelled using logistic regression. Thus, only 273/411 positive triplicates representing triplicates where the indicator sample of the triplicate is the first positive sample were included in this model. Repeating the model using all the 411 triplicates and adjusting for repeated measurements did not change the results.
** Factors included in the table are selected using multivariate logistic regression. Other factors included in the models were: age, gender, type of transplantation (solid organ transplantation vs haematopoietic stem cell transplantation).
***273 IU/mL is the lower limit of quantification for the used CMV PCR kit.

Figure 3

Forest plot of HR [95% CI] for a first CMV infection after transplantation



*Time dependent variables were updated accordingly, and death was included as a competing risk. The model also included age, gender, calendar year, and adjusted for type of transplantation (kidney, liver, heart, lung, myeloablative conditioning transplantation, non-myeloablative conditioning and umbilical cord blood transplantations). Compared to kidney recipients, lung and umbilical cord blood transplantation recipients had an increased HR of subsequent CMV infection (lung(HR1.5 [95% CI 1.03-2.3], p=0.03) and umbilical blood cord (HR 4.3 [95% CI 1.6-12.0], p=0.004) respectively).
**For solid organ transplantation recipients CMV igG D+/R- is associated with a high risk of CMV infection while D-/R+ is associated with a low risk. Amongst bone marrow transplant recipients, D-/R+ is associated with a high risk of CMV infection whereas D+/R- is associated with a low risk. For both types of transplantation, D+/R- is associated with intermediary risk of CMV infection.

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