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MATCH
Management of Post-Transplant Infections in Collaborating Hospitals

Use of First Positive Cytomegalovirus (CMV) PCR Determination to Differentiate a Viral Blip from Established CMV Infection in Transplant Recipients

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BACKGROUND

CMV infection frequently complicates the course after solid organ or haematopoietic stem cell transplantation. A pre-emptive strategy relies on regular screening with CMV PCR of recipients to diagnose and promptly treat the infection while still asymptomatic. The PCR technology is known in HIV to also identify isolated positive reads – so called blips – that do not require medical intervention. Whether such viral blips exist also for CMV in the transplantation setting remains unknown. We wanted to determine the prevalence and risk factors for developing viral blips in screening with CMV PCR of transplant recipients.

METHODS

In a large unselected cohort of transplant recipients, consecutive situations were identified characterised by a triplicate of CMV PCRs during follow-up (**Figure 1**) where the 1st PCR was undetectably low, the 2nd was positive and the interval between the 2nd and 3rd PCR was < 8 days apart. The situation was called a PCR triplet, and was defined as either a viral blip or an established infection depending on whether the 3rd PCR was again undetectably low or still positive, respectively. Using logistic regression, the impact of the following factors on the % of PCR triplets being classified as blips were investigated: viral load of the 2nd PCR, type of transplantation, risk of CMV infection associated with CMV IgG serostatus of donor and recipient, and use of treatment.

Figure 1

Inclusion Criteria and Definition of a CMV Blip

Criteria for PCR triplet:
- 1st PCR: Always negative
- 2nd PCR: Always positive
- 3rd PCR: Either positive or negative
- Δt between 2nd PCR and 3rd PCR < 8 days

If positive → confirmation of on going CMV replication

If negative→ detection of a **CMV Blip**

Patient criteria:
- Solid organ transplant (SOT) or haematopoietic stem cell transplantation (HSCT) recipients transplanted between 2003-2013
- Serostatus of D+/R+, D+/R- or D-/R+
- Minimum one positive CMV PCR (e.g. 2nd PCR ≥ 273 IU/mL) within the first 12 months following transplantation, according to criteria described above for PCR triplet

Table 1

Characteristics of 251 transplant recipients that constitute the 402 PCR triplets

Characteristics	
Median age (IQR), years	51 (40-60)
Gender (% males)	167 (75%)
Type of transplantation (n)	
SOT recipients	126 (50%)
HSCT recipients	125 (50%)
Risk of CMV infection according to CMV IgG status* (n)	
High risk of CMV infection	122 (49%)
Intermediary risk of CMV infection	110 (44%)
Low risk of CMV infection	19 (8%)

* 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 associatedwith high risk of CMV infection, while D-/R+ is associated with low risk. Amongst bone marrow transplant recipients, D-/R+ is associatedwith a high risk of CMV infection, whereas D+/R- is associated with a low risk. For both types of transplantation, D+/R+ is associatedwith intermediary risk of CMV infection.
Abbreviations: IQR; inter quartile range, CMV; Cytomegalovirus, SOT; solid organ transplantation, HSCT; haematopoietic stem cell transplantation.

RESULTS

Of a total of 402 PCR triplets (corresponding to 251 unique patients, **Table 1**) fulfilling the criteria above, 126 were classified as blips (31%). The proportion of blips was higher the lower the viral load of the 2nd PCR (**Figure 2**); the adjusted odds ratio (OR) of a blip (versus 2nd PCR just positive = 273 IU/mL) was 0.12 ([0.04-0.4] p<0.001), and 0.03 ([0.003-0.2] p<0.001) when viral load was 2,730-9,100 or > 9,100 IU/mL, respectively (**Figure 3**). However, the OR was comparable with the group just positive if viral load levels were 273-2,730 IU/mL (**Figure 3**). The results were unaffected by use of anti CMV treatment (data not shown).

CONCLUSION

Viral blips are frequent while screening transplant recipients with CMV PCR, in particular if the viral load of the first positive PCR (i.e. the "2nd PCR" in our model) is low. Our findings imply that in asymptomatic patients, a first positive CMV PCR viral load < 2,730 IU/mL should be confirmed before initiation of antiviral therapy. Otherwise, more than 40% of patients will receive unnecessary antiviral medication.

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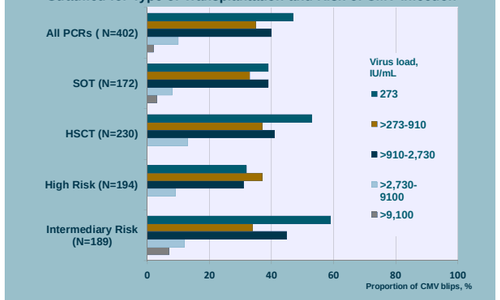
Figure 2

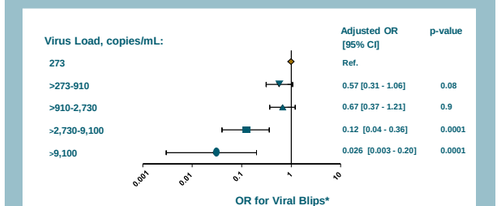
Proportion of CMV Blips in Different Intervals of CMV Virus Load, Stratified for Type of Transplantation and Risk of CMV Infection*



* Data from low-risk patients not shown in graph due to the small sample size (N=19)

Figure 3

Odds Ratio (OR) for Viral Blips According to Virus Load in the First Positive PCR



*Adjusted for type of transplantation, sex, age at transplantation, use of antiviral treatment between 2nd PCR and 3rd PCR, and risk associated with donor (D) and recipient (R) serostatus

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