IDSA 2009

Post-transplant CMV-Infection: Therapeutic and Immunological Risk Factors

C da Cunha-Bang[1,2], SS Sørensen[3], M Iversen[4], SA Mortensen[4], H Sengeløv[5], JG Hillingsø[6], Z Fox[7], JD Lundgren[1,2]

The Herpes Virus Transplantation Study Group at the State University Hospital (*Rigshospitalet*) . State University Hospital & University of Copenhagen, Denmark

[1]Copenhagen HIV Programme, University of Copenhagen, Denmark, [2]Department of Clinical Microbiology, Rigshospitalet, University of Copenhagen, Denmark, [3]Department of Nephrology, Rigshospitalet, University of Copenhagen, Denmark, [4]Department of Cardiology, Division of Heart and Lung Transplantation, Rigshospitalet, University of Copenhagen, Denmark, [5]Department of Haematology Rigshospitalet, University of Copenhagen, Denmark, [6]Department of Surgery C, Rigshospitalet, University of Copenhagen, Denmark, [7]University College Medical School, Royal Free Campus, London, United Kingdom

Caspar da Cunha-Bang, MD
Copenhagen HIV Programme, CHIP
University of Copenhagen, Faculty of Health Sciences
The Panum Institute/Building 21.1, Blegdamsvej 3B
DK-2200 Copenhagen N
Tel: + 45 35 45 57 57
Fax:+ 45 35 35 57 58
E-mail: cdb@cphiv.dk

BACKGROUND

- Post-transplantation Cytomegalovirus(CMV)-infection remains a potentially serious complication to immunosuppression with risk of progression to CMV- disease
- There is currently no consensus on approach to the prevention of CMV-disease
- Pathogenesis and risk factors for CMV-disease are well described, however few studies address individual combinable risk factors for predisposing CMV-infection

OBJECTIVES

- To investigate pre- and post-transplantation variables and their association with risk of CMV-infection within the first 12 months of transplantation in a cohort of solid organ (Heart, Kidney, Liver, Lung) and bone marrow transplant patients

METHODS

Patients and study design

- Consecutive patients transplanted between 2004-2007 and routinely screened for CMV-infection by a minimum of 3 CMV-PCR measurements within the first 12 months of transplantation were included
- Data was extracted from electronic health records, retrospectively

CMV-DNA

- Detection of CMV-DNA was performed in the Department of Clinical Microbiology at Rigshospitalet. The analyses were done on EDTA-blood using the Cobas Amplicor monitor PCR test

Endpoint definition

- CMV-infection was defined a priori to be present if a patient had two consecutive CMV-PCR measurements above lowest limit of detection (300 copies/mL) or alternatively one CMV-PCR › 3000 copies/mL

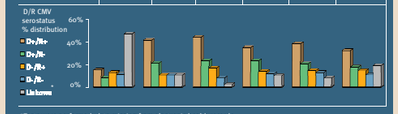
Statistical methods

- Time to CMV-infection was investigated using Cox proportional hazards analysis; both fixed-time and time-updated variables were explored
- The following fixed-time variables were included in the Cox models: Type of transplantation, Donor(D)/Recipient(R) CMV serostatus, gender, age, prior transplantation and year of transplantation
- The following time-updated variables were included in the Cox models: Use of immunosuppressive drugs and use of anti-CMV drugs
- Subgroup analyses were performed on patients who had a solid organ transplantation and among patients with known Donor/Recipient CMV serostatus

Table 1

Baseline Characteristics

Type of Transplant number	Bone marrow N=119	Heart N=9	Kidney N=104	Liver N=48	Lung N=97	Total N=377
Gender: N (%)						
Male	48 (40.3%)	2 (22.2%)	44 (42.3%)	25 (52.1%)	52 (53.6%)	171 (45.4%)
Female:	71 (59.7%)	7 (77.8%)	60 (57.7%)	23 (47.9%)	45 (46.4%)	206 (54.6%)
Age at transplantation median years (IQR)	23 (11, 42)	52 (41, 57)	40 (31, 54)	40 (11, 54)	51 (35, 58)	39 (23, 54)



*Tests were performed, data missing from electronic health records

Figure 1

CMV-infection endpoints and time to event

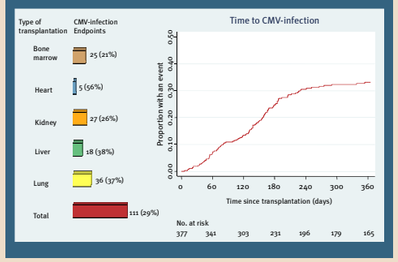
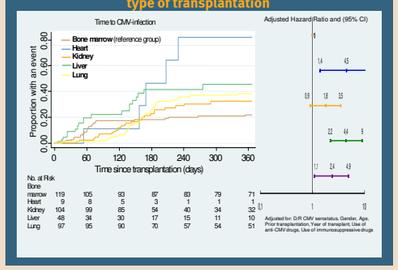


Figure 2

Time to and risk of CMV-infection according to type of transplantation



RESULTS

Tables and figures

- In total 377 patients were included in the study. The Baseline characteristics for all patients are shown in **Table 1**
- There were a total of 111 patients with CMV-infection endpoints, the distribution between the type of transplantation and time to CMV-infection is shown in **Figure 1**
- The risk of CMV-infection was higher for all types of solid organ transplantations compared with bone marrow transplantation (**Figure 2**)
- In sub-group analysis of solid organ transplantation the highest risk of CMV-infection was seen in transplantations where the donor was CMV serostatus positive (**Figure 3**)
- The risk of CMV-infection was increased when patients were using immunosuppressive drugs and it was reduced when patients were using anti-CMV drugs (**Figure 4**)
- Among patients given and patients not given anti-CMV chemoprophylaxis, comparable numbers developed CMV-infection (**Figure 5**)

SUMMARY

- The risk of CMV-infection was higher among recipients of all forms of solid organ transplantation compared with bone marrow transplantation
- In solid organ transplantation the risk of CMV-infection was highest for CMV serostatus combination D+/R-
- When the recipient was CMV serostatus positive the risk of CMV-infection was 80% higher if the donor was CMV serostatus positive versus negative
- The risk of CMV-infection was increased while using immunosuppressive drugs
- Anti-CMV drugs reduced the risk of CMV-infection by 70% while actively used, but appears to merely postpone the onset of this event rather than preventing it

CONCLUSION

- Use of anti-CMV chemoprophylaxis may possibly be restricted to donor CMV serostatus positive transplantations where the risk of CMV-infection is highest
- In these cases the duration of anti-CMV chemoprophylaxis should possibly be extended beyond the current standard of care
- Preemptive treatment may possibly be the optimal intervention in donor CMV serostatus negative transplantations where the risk of CMV-infection is lower
- Effects and risks from stratification of anti-CMV intervention as outlined above should be evaluated in future clinical trials

Figure 3

Subgroup analysis - solid organ transplantation – time to and risk of CMV-infection acording to D/R CMV serostatus

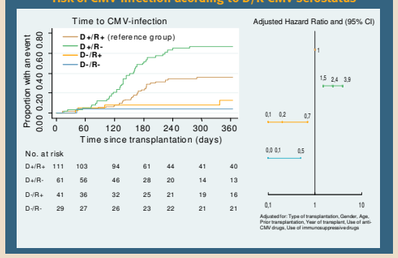
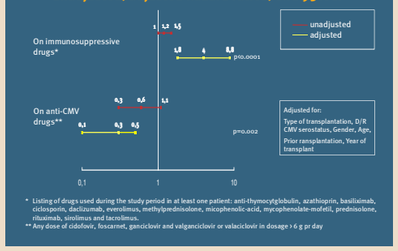


Figure 4

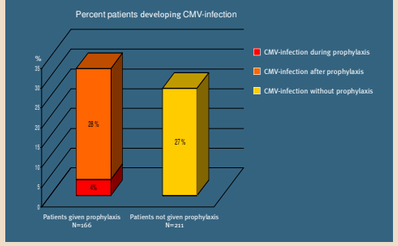
Risk of CMV-infection; time-updated variables unadjusted, adjusted hazard ratios, and 95%CI



* Listing of drugs used during the study period in at least one patient: anti-thymocyte/globulin, azathioprin, basiliximab, ciclosporin, daclizumab, everolimus, methylprednisolone, micophenolic-acid, mycophenolate-mofetil, prednisolone, rituximab, sirolimus and tacrolimus.
** Any dose of cidofovir, foscarnet, ganciclovir and valganciclovir or valaciclovir in dosage › 6 g pr day

Figure 5

CMV-infection in patients given and not given anti-CMV chemoprophylaxis



Download poster at: www.cphiv.dk

CHIP COPENHAGEN HIV PROGRAMME