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EBV DNAemia and Post-transplant Lymphoproliferative Disorders (PTLD) among Transplant Recipients

N E.Wareham[1], C Heilmann[2], H Sengeløv[3], S Schwartz Sørensen[4], F Gustafsson[5], M Iversen[5], A Rasmussen[6], C Da Cunha-Bang[7], J D Lundgren[1]

on behalf of MATCH in PERSIMUNE study group

[1]CHIP, Department of Infectious Diseases, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [2]Department of Paediatrics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [3]Department of Haematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [4]Department of Nephrology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [5]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [6]Department of Surgical Gastroenterology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [7]Department of Haematology, Roskilde Hospital, Roskilde, Denmark

Neval E. Wareham, MD, PhD Student
Rigshospitalet, University of Copenhagen
CHIP, Department of Infectious Diseases, Section 2100
Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark
Tel: + 45 35 45 57 97
Fax: +45 35 45 57 58
E-mail: neval.ete.wareham@regionh.dk

MATCH
Management of Post-Transplant Infections in Collaborating Hospitals

BACKGROUND

- EBV-associated PTLD is a potentially life-threatening complication to transplantation[1, 2].
- Early detection and early intervention of PTLD offers the best potential for a positive outcome[2, 3, 4].
- Regular screening for cell-free circulating EBV DNA may enable early detection of emerging PTLD[3].
- The benefit of a pre-emptive strategy based on regular screening for EBV DNA and early treatment is unknown.

AIMS

- To compare dynamics of EBV DNAemia episodes among solid organ (SOT) and hematopoietic stem cell (HSCT) transplant recipients and the extent that such episodes were associated with the development of PTLD.

METHODS

- Consecutive SOT and HSCT recipients at our hospital, transplanted between January 2011 and April 2015 were included.
- First EBV DNAemia episode, defined as two consecutive EBV DNA PCR ≥500 copies/mL measured in plasma and taken within 14 days, was identified.
- The first EBV DNAemia episodes were characterized clinically and virologically and doubling times were calculated according to standard methods[5] (**Figure 1**).
- Development of PTLD in relation to the EBV DNAemia episodes was also explored.

Figure 1

Calculation of EBV doubling time of EBV DNAemia episodes, using standard methods[5]

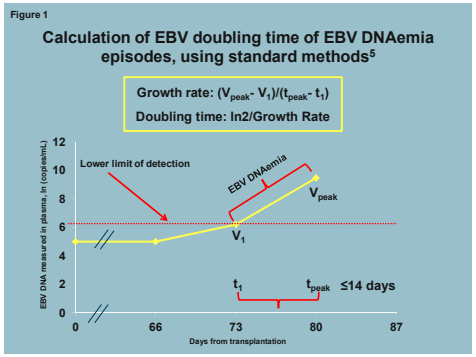

Table 1

Characteristics of recipients with subsequent EBV DNAemia, according to type of transplantation

Characteristics	All Recipients	Type of transplantation		P-value
		Solid Organ	Hematopoietic Stem Cell	
Number (%) of recipients in the cohort	1179 (100)	755 (64)	424(36)	
Number (%) of recipients with EBV DNAemia	59 (5)	17 (2)	42 (10)	≤0.0001
Median age at time of transplantation (IQR), years	12 (6-46)	19 (8-53)	11 (5-40)	0.2
Gender (% male)	71%	59%	76%	0.2
Median time-span from transplantation to first EBV DNA (IQR), days	74 (44-171)	116 (74-208)	62 (42-113)	0.03
Number (%) of recipients with development of PTLD among recipients with EBV DNAemia	21 (36%)	5 (29%)	16 (38%)	0.4

RESULTS

Prevalence of EBV DNAemia episodes among recipients screened for EBV DNA

- A total of 59 episodes of first EBV DNAemia was diagnosed in 1179 recipients transplanted since January 2011 (5%).
- HSCT recipients were screened more intensively than SOT.
- EBV DNAemia episodes were seen more frequently in HSCT vs SOT recipients (10% (42/424) vs 2% (17/755), respectively), and observed earlier in relation to time of the transplantation (**Table 1**).

Prevalence and characteristics of PTLD

- 21 of 59 (36%) recipients developed PTLD in relation to their first EBV DNAemia episode.
- PTLD was diagnosed a median of 10 days after EBV DNAemia was first detected (**Table 2**).

Table 2

Characteristics of recipients who develop PTLD or not among recipients with EBV DNAemia (N=59)

Characteristics	PTLD	No PTLD	p-value
Number of recipients	21	38	
Median age at transplantation (IQR), years	24 (8-60)	11 (5-40)	0.2
Proportion of males	81%	66%	0.2
Type of transplantation: Proportion of SOT Proportion of HSCT	 29% 38%	 71% 62%	 0.4 0.4
Median time-span from first EBV DNAemia to PTLD (IQR), days	10 (1-27)	-	-
Median viral load (cop/mL), (IQR), first EBV DNA in the EBV DNAemia episode	1,900 (500-11,500)	500 (500-930)	0.004
Median viral load (cop/mL), (IQR), peak EBV DNA in the EBV DNAemia episode	53,000 (3,400-89,500)	650 (500-3,400)	<0.0001
Proportion of recipients with EBV DNA at the lower limit of detection (500 cop/mL), first EBV DNA in the EBV DNAemia episode	38%	66%	0.06
Proportion of recipients with a negative EBV DNA tested ≤7 days prior to the EBV DNAemia episode	43%	47%	0.4
Median EBV Doubling time (IQR), days	1.6 (1.0-4.9) (N=16)	3.4 (1.5-21.8) (N=13)	0.1

- Factors associated with the occurrence of PLTD in relation to the EBV DNAemia episode were:
- Higher first and peak EBV DNAemia levels.
- The first EBV DNAemia level was at the lower limit of detection in 38%, and 43% had been screened with a negative test within 7 days previously – and comparable for those with and without PTLD.
- EBV DNAemia doubling time was calculated for 29 episodes. Median doubling time was 2.3 days and did not differ for those with and without PTLD.

CONCLUSION

- EBV DNAemia episodes were observed rarely in transplant recipients; 36% of the episodes were associated with the emergence of PTLD
- No factor examined was able to reliably differentiate those with and without PTLD (**Table 2**).
- The doubling time of EBV DNAemia during the episode was short (2 days). Thus, screening intervals for EBV DNA needs to be < 7 days to diagnose the episodes in a cohort[5] while EBV DNAemia remains low; this may not be feasible in most settings.
- More sensitive and discriminatory tools are, thus required in order to detect early stages of PTLD.

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chip Centre for Health & Infectious Disease Research

REGION H Rigshospitalet

Faculty of Health Sciences University of Copenhagen

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