GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

MALATTIA LINFOPROLIFERATIVA POST-TRAPIANTO

FAD SINCRONA
4 dicembre 2024

con il patrocinio di: S·I·T·O· SOCIETÀ ITALIANA DEI TRAPIANTI D'ORGANO E DI TESSUTI

PTLD: strategie di prevenzione e monitoraggio nelle diverse tipologie di trapianto. Immunosoppressione, infezioni concomitanti e profilassi antivirale

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PLTD: differences in incidence and time distribution in allo-HSCT and SOT

HSCT

- 0.1-63%. EBMT study:3.2% (1.2% in MRD->11.2% in MMUD)
- Median time from transplantation: 2-4 months (4% later than 12 months)
- Almost 100% of PTLD cases are associated with EBV
- Generally derives from the donor's B lymphocytes

About 20.000 allo-HSCT per year in Europe.

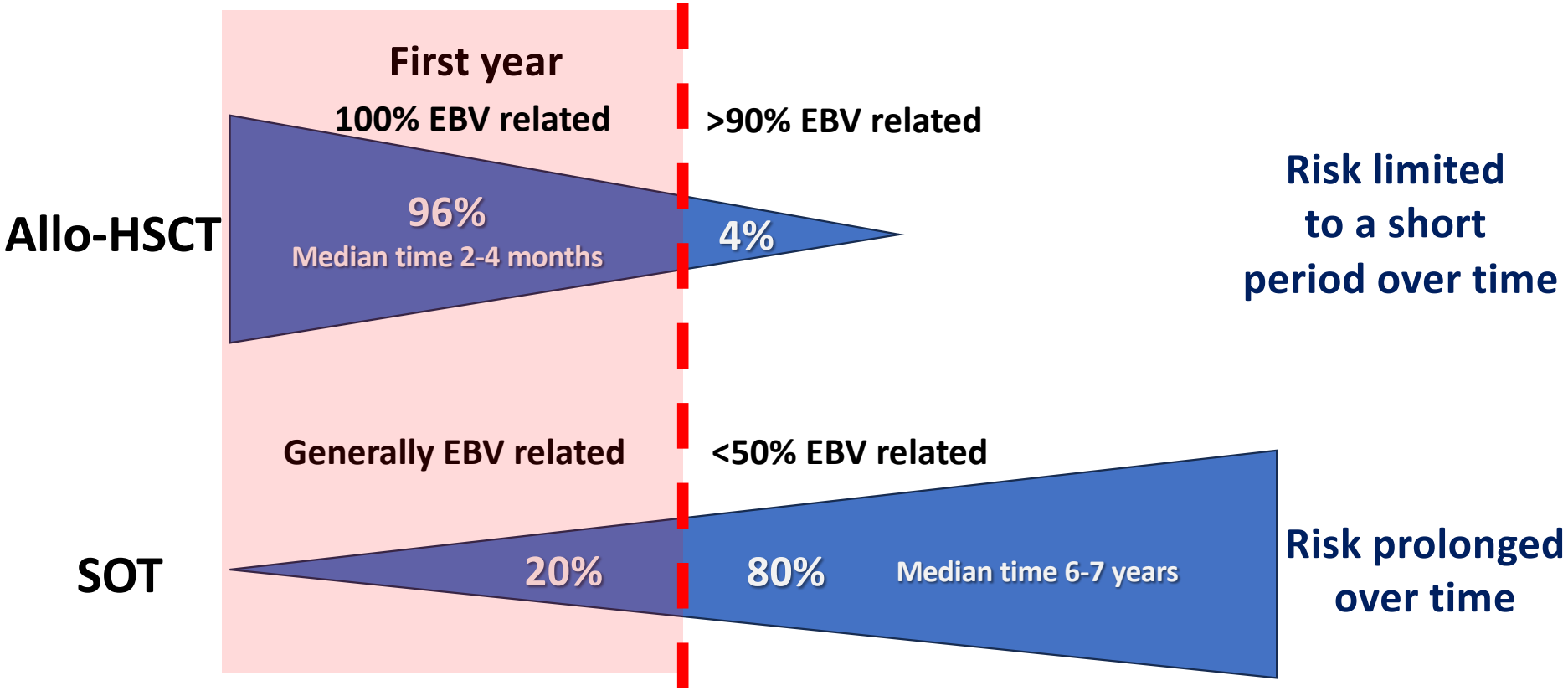
SOT

- 1-33%. Spain study: 1.8% (1.4% in kidney->16.4% in multivisceral transplantation)
- Median time from transplantation: 6.7 y (21% within12 months)
- ~50% of PTLD cases are associated with EBV
- Generally derives from the recipient's B lymphocytes

About 28.000 SOT per year in Europe.

Styczynski, et al. Haematologica 2016;101:803-11 – Jimenez Ubieto et al Blood 2023;142:4490-2 - Tichadou et al Blood 2023; 142:443-5

EBV/PTLD in allo-HSCT and SOT: different epidemiology, different monitoring strategy



cancers Cancers 2022, 14, 5949. MDPI

Review

Recent Advances in Adult Post-Transplant Lymphoproliferative Disorder

Mariam Markouli [1], Fauzia Ullah [2], Najiullah Omar [2], Anna Apostolopoulou [3], Puneet Dhillon [4], Panagiotis Diamantopoulos [1], Joshua Dower [5], Carmelo Gurnari [2], Sairah Ahmed [6,†] and Danai Dima [2,7,*,†]

Table 2. Risk factors for PTLD.

Post-SOT	Post-alloHSCT
Strong Evidence:	**Strong Evidence:**
1. Type of Graft: Intestinal > Lung > Heart > others Multivisceral grafts or graft from deceased donors 2. EBV Seronegative/naive EBV recipient pre-SOT 3. High intensity IST 4. Anti-thymocyte globulin use as part of induction IST	1. High degree of HLA mismatch HLA-mismatched or unrelated donor Haploidentical donor Umbilical cord blood graft use 2. Type of conditioning regimen T-cell-depleting strategies (in vivo and ex vivo) Anti-thymocyte globulin use Non-myeloablative conditioning regimens 3. Recipient old age > 50 years
Weak Evidence:	**Weak Evidence:**
a. Non-white ethnicity b. Young recipient and old donor age c. Non-EBV infection d. Recipient HLA-A26 and B38 status	a. Acute GVHD b. History of splenectomy c. Diagnosis of Aplastic Anemia d. Non-EBV infection

Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines

Jan Styczynski,[1] Walter van der Velden,[2] Christopher P. Fox,[3] Dan Engelhard,[4] Rafael de la Camara,[5] Catherine Cordonnier,[6] and Per Ljungman[7] on behalf of the Sixth European Conference on Infections in Leukemia, a joint venture of the Infectious Diseases Working Party of the European Society of Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN)

Haematologica 2016
Volume 101(7):803-811

Major risk factors for clinically significant EBV reactivation after allo-HSCT.

- **T-cell depletion (in vivo, ex vivo)**
- **EBV serology**
- **HLA mismatch**
- **Severe acute or chronic GvHD**

Table 3. Risk factors for EBV-PTLD after HSCT.

Pre-transplant risk factors
• T-cell depletion (either *in vivo* or *ex vivo*)
• EBV serology donor/recipient mismatch
• Cord blood transplantation (CBT)
• HLA mismatch
• Splenectomy
• Second HSCT
Post-transplant risk factors
• Severe acute (especially steroid-refractory) or chronic GvHD requiring intensive immunosuppressive therapy
• High or rising EBV viral load
• Treatment with mesenchymal stem cells

Biol Blood Marrow Transplant 25 (2019) 1441 – 1449

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Analysis

Risk Factors and Predictive Scoring System For Post-Transplant Lymphoproliferative Disorder after Hematopoietic Stem Cell Transplantation

Ayumi Fujimoto[1,2], Nobuhiro Hiramoto[2], Satoshi Yamasaki[3], Yoshihiro Inamoto[4], Naoyuki Uchida[5], Tetsuo Maeda[6], Takehiko Mori[7], Yoshinobu Kanda[8], Tadakazu Kondo[9], Souichi Shiratori[10], Shigesaburo Miyakoshi[11], Ken Ishiyama[12], Kazuhiro Ikegame[13], Yoshiko Matsuhashi[14], Junj

Table 2
Characteristics of Allogeneic HSCT

Variable	No PTLD Group (N = 39,928)	PTLD Group (N = 267)
Conditioning regimen, n (%)		
MAC	23,680 (60)	123 (47)
RIC	16,144 (40)	140 (53)
Unknown	104 (0)	4 (0)
Donor type, n (%)		
MRD	13,034 (33)	24 (9)
MMRD	4043 (10)	52 (19)
MURD	10,135 (25)	81 (30)
MMURD	1977 (5)	16 (6)
CB	10,030 (25)	88 (33)
Unknown	709 (2)	6 (2)
Stem cell source, (%)		
BM	20,063 (50)	126 (47)
PB	9660 (24)	52 (19)
CB	10,030 (25)	88 (33)
Other/unknown	175 (0)/3 (0)	1 (0)/0 (0)
GVHD prophylaxis, n (%)		
CSP-based	18,216 (46)	88 (33)
TAC-based	20,593 (52)	172 (64)
Other	637 (2)	4 (2)
None/unknown	274 (0)/208 (0)	0 (0)/3 (1)
Use of ATG, n (%)	3915 (10)	111 (42)
Conditioning only	3299 (8)	94 (35)
GVHD prophylaxis only	70 (0)	1 (0)
Acute GVHD treatment only	303 (1)	6 (2)
Two or more	234 (1)	10 (4)
No/unknown	35,870 (90)/152 (0)	152 (57)/4 (2)
Use of alemtuzumab, n (%)	45/38,895 (<1)	0/251 (0)
Use of ex vivo TCD, n (%)	291/38,766 (<1)	5/264 (2)
Acute GVHD grade II-IV (%)		
Yes	13,797 (35)	115 (43)
No/unknown	22,784 (57)/3347 (8)	142 (53)/10 (4)
Chronic GVHD		
Yes	12,150 (30)	88 (33)
No/unknown	18,298 (46)/9480 (24)	146 (55)/33 (12)

Table 3
Univariate and Multivariate Analyses for the Development of PTLD

Variable	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	P	HR	(95% CI)	P
Year of HSCT						
1990–2009	1.00			1.00		
2010–2015	2.77	(2.13-3.61)	<.001	1.87	(1.38-2.52)	<.001
Disease						
AML/MDS	1.00			1.00		
ALL	.99	(.69-1.44)	.98	1.08	(.75-1.57)	.68
CML/MPD	.94	(.56-1.57)	.81	1.55	(.89- 2.69)	.12
Lymphoid malignancies	1.24	(.88-1.75)	.22	1.33	(.92-1.92)	.13
AA	4.95	(3.47-7.07)	<.001	5.19	(3.32-8.11)	<.001
Others	1.91	(.97-3.76)	.06	1.94	(.97-3.89)	.06
Conditioning regimen						
MAC	1.00			1.00		
RIC	2.00	(1.56-2.55)	<.001	.82	(.60-1.12)	.22
Donor type						
MRD	1.00			1.00		
MMRD	10.4	(6.35-17.1)	<.001	4.39	(2.39-8.07)	<.001
MURD	4.89	(3.07-7.79)	<.001	4.08	(2.39-6.99)	<.001
MMURD	5.46	(2.88-10.3)	<.001	3.20	(1.58-6.47)	.001
CB	7.24	(4.56-11.5)	<.001	8.03	(4.72-13.7)	<.001
Number of allogeneic HSCT						
Two or more	2.15	(1.56-2.97)	<.001	1.50	(1.05-2.15)	.03
GVHD prophylaxis						
CSP-based	1.00			1.00		
TAC-based	2.07	(1.59-2.69)	<.001	.82	(.59-1.12)	.21
ATG in a conditioning regimen						
Yes	7.76	(6.03-9.99)	<.001	6.13	(4.33-8.68)	<.001
ATG for GVHD treatment*						
Yes	6.87	(4.00-11.8)	<.001	2.09	(1.17-3.72)	.01
Acute GVHD grade II-IV*						
Yes	1.83	(1.43-2.35)	<.001	1.93	(1.48-2.52)	<.001

* ATG for GVHD treatment and acute GVHD grade II-IV were treated as time-dependent variables.

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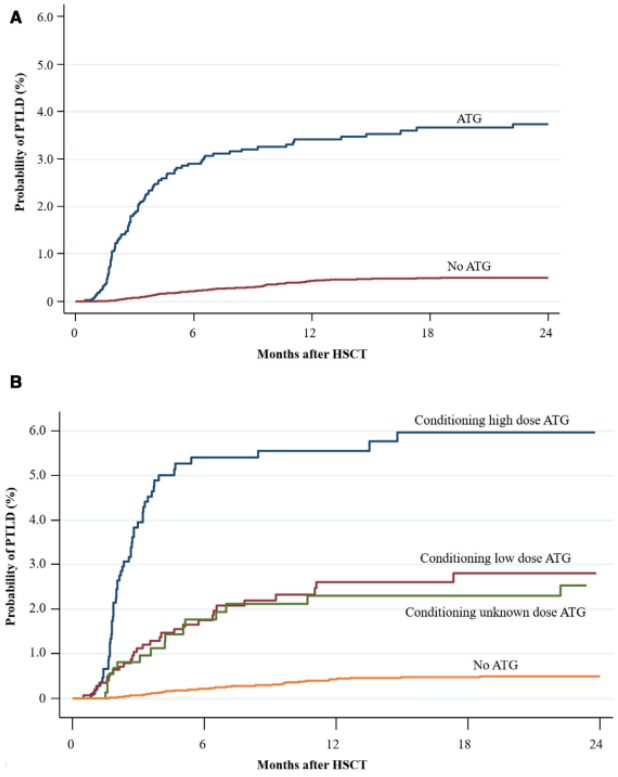

Figure 3. Probability of PTLD with the use of ATG in conditioning. (A) The probability of PTLD was significantly higher in patients who received ATG. (B) Receipt of high-dose ATG (total dose >2.5 mg/kg Thymoglobulin or >5.0 mg/kg ATG-F) was associated with a significantly higher risk of developing PTLD. By 2 years after HSCT, PTLD developed in 6.0% of patients who received high-dose ATG and in 2.8% of those who received low-dose ATG.

PTLD incidence: 0.66%

Risk factor	Point(s)
ATG use	
High-dose	2
Low-dose	1
Donor type	
MMRD	1
MURD	1
MMURD	1
CB	2
Disease	
AA	1

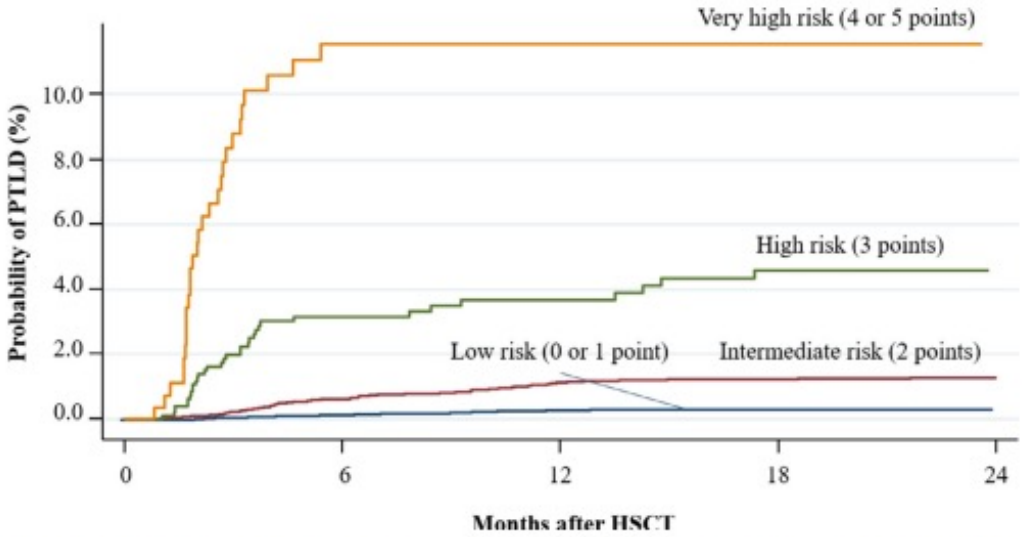

Figure 4. Probability of PTLD by the risk scoring system. Points were assigned for each risk factor as follows: high-dose ATG use, 2 points; low-dose ATG use, 1 point; MMRD, 1 point, MURD, 1 point; MMURD, 1 point; CB, 2 points, and AA, 1 point. The sum of points was used to classify risk groups: 0 or 1 point, low risk; 2 points, intermediate risk; 3 points, high risk; and 4 or 5 points, very high risk. The very-high-risk and high-risk groups had a markedly greater risk of developing PTLD, with probabilities of PTLD at 2 years after HSCT in these risk groups of 11.5% and 4.6%, respectively.

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SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES
Clinical TRANSPLANTATION WILEY

Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Upton D. Allen[1,2,3] | Jutta K. Preiksaitis[4] | on behalf of the AST Infectious Diseases Community of Practice

TABLE 1 Risk Factors for PTLD in solid organ transplant recipients

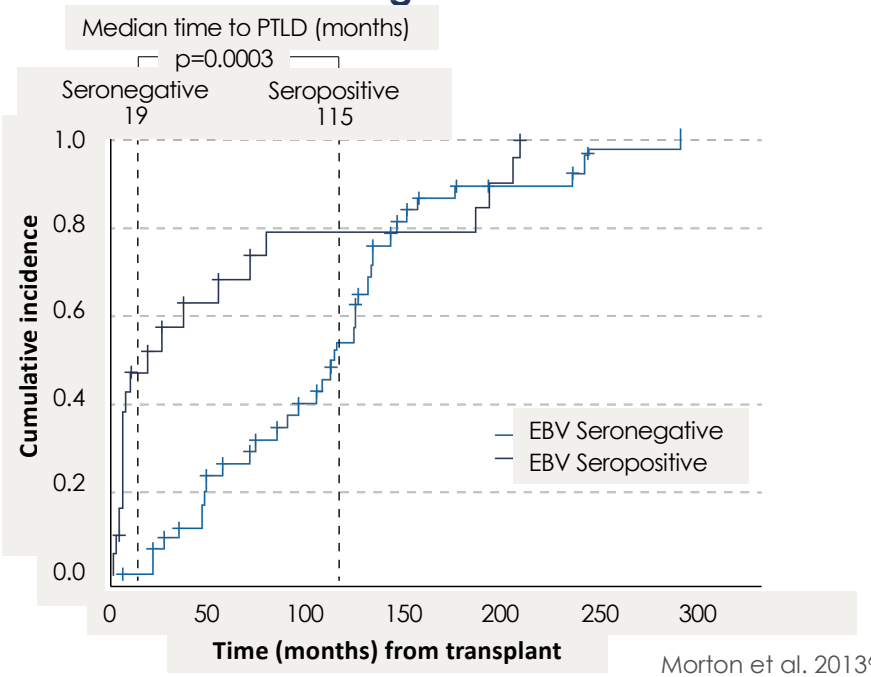
Early PTLD
Primary EBV infection
Type of organ transplanted (intestine > lung>heart > liver>pancreas > kidney)
Polyclonal anti-lymphocyte antibodies[a]
Young recipient age (ie, infants and young children)
Late PTLD
Duration of immunosuppression
Type of organ transplanted
Older recipient age (ie, adults)

- An overwhelming risk factor in most analyses is EBV-seronegativity pre-transplant and primary EBV infection, placing pediatric populations at higher risk of developing PTLD than their adult counterparts
- An increased risk associated with being EBV sero-negative in kidney (HR 3.6), and heart (HR 4.0) but found a smaller but significantly increased risk in seronegative liver recipients (HR 1.5).
- Among seronegative pediatric recipients donor seropositivity (D+R−) and donor seronegativity (D−R−) resulted in comparable risks for PTLD at three years post-transplant, perhaps reflecting the high rate of community-acquired infection in children.
- In contrast, in seronegative adult recipients D−R− recipients trended toward having a lower risk of PTLD than D+R− recipients which received statistical significance when a living donor was used.
- Intestinal transplant recipients appear to have an exceptional high risk of PTLD development, independent of pre-transplant EBV serostatus

EBV status and PTLD development post-SOT

- Pre-transplant EBV seronegativity increases the incidence of PTLD from 10- to 75-fold over that of EBV-seropositive recipients[1,2]

Time to PTLD onset according to EBV status at the time of transplantation[3]



Morton et al. 2013[6]

EBV, Epstein–Barr virus; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. Walker RC, et al. Clin Infect Dis. 1995;20:1346–1353; 2. Cockfield SM. Transpl Infect Dis. 2001;3:70–78; 3. Morton M, et al. Transplantation. 2013;95:470–480.

Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines

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- Prospective monitoring of EBV DNA performed by quantitative PCR is recommended.
- Screening for EBV DNA-emia should start within the first month after allo-HSCT. However, the incidence of EBV-PTLD during the first month after HSCT is estimated to be below 0.2%. Monitoring should continue for at least 4 months after HSCT, with a frequency of at least once a week.
- As the calculated doubling time for EBV might be as short as hours, more frequent sampling in patients with rising EBV DNA-emia may be warranted

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY *Clinical Transplantation.* 2019;33:e13652.

Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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- Studies of the sensitivity and specificity of quantitative EBV viral load for the diagnosis of early PTLD and symptomatic EBV infection are limited
- The use of EBV viral load as a diagnostic test has good sensitivity for detecting EBV-positive early PTLD but misses EBV-negative as well as some cases of localized and donor-derived EBV + PTLD
- However, it had poor specificity, resulting in good negative (greater than 90%) but poor positive predictive value (as low as 28% and not greater than 65%) in these populations
- Elevated and often sustained elevation in EBV loads has been observed in 67%-72% of adult liver, 31%-29% of adult kidney, and 13%-42% (assay dependent) of adult lung transplant recipient EBV-seropositive pre-transplant and appears to be a poor marker of future PTLD risk.

Challenging issues in the monitoring of EBV/PTLD in allo-HSCT and SOT

- Allo-HSCT
  - Variable risk but in a short time period
  - EBV-DNAemi is a sensitive marker of future PTLD
  - DNAemia monitoring intensification during the first months from transplant in all transplants
  - In the clinical practice EBV-DNAemia monitoring associated to CMV DNAemia monitoring
- SOT
  - EBV-DNAemia is a good marker of early PTLD in seronegative children and in very high risk SOTs (i.e. intestinal and multivisceral transplant)
  - EBV-DNAemia is a poor marker of late PTLD
  - Considering the prolonged risk over time, it is difficult to define how prolonged should be the virological monitoring.
  - In view of the lack of a good marker for virological monitoring clinical suspicion of late PTLD is crucial

Journal of the Pediatric Infectious Diseases Society
SUPPLEMENT ARTICLE

A Focused Review of Epstein-Barr Virus Infections and PTLD in Pediatric Transplant Recipients: Guidance From the IPTA and ECIL Guidelines

Masaki Yamada,[1,†,©] Arnaud G. L'Huillier,[2,3,†] and Michael Green[4,5]

Table 2. Guideline-Endorsed Recommendations for the Prevention of EBV Disease and PTLD [1, 6].

	SOT[a1]	HCT[b2]
Prophylaxis		
Chemoprophylaxis—Antivirals	Not recommended *(weak/moderate to prevent EBV infection)* *(strong/moderate to prevent EBV disease)*	Not recommended *(DII)*
Immunoprophylaxis		
Vaccines	Unavailable	
IVIG	Not recommended *(weak/moderate)*	Not recommended *(DIII)*
Anti-CD20	Not recommended *(strong/low)*	Marginally recommended *(CII)*
VSTs	Not recommended	Marginally recommended *(CII)*
Preemptive therapy		
Reduction of immunosuppression	Recommended *(strong/moderate for liver)* *(weak/low for other organs)*	Recommended when combined with anti-CD20 *(AII)*
Chemoprophylaxis—Antivirals	Not recommended *(weak/low)*	Not recommended *(DIII)*
Immunoprophylaxis		
Anti-CD20	Not recommended *(weak/very low)*	Recommended, alongside RIS whenever possible *(AII)*
VSTs	Not recommended *(weak/low)*	Marginally recommended *(CII)*

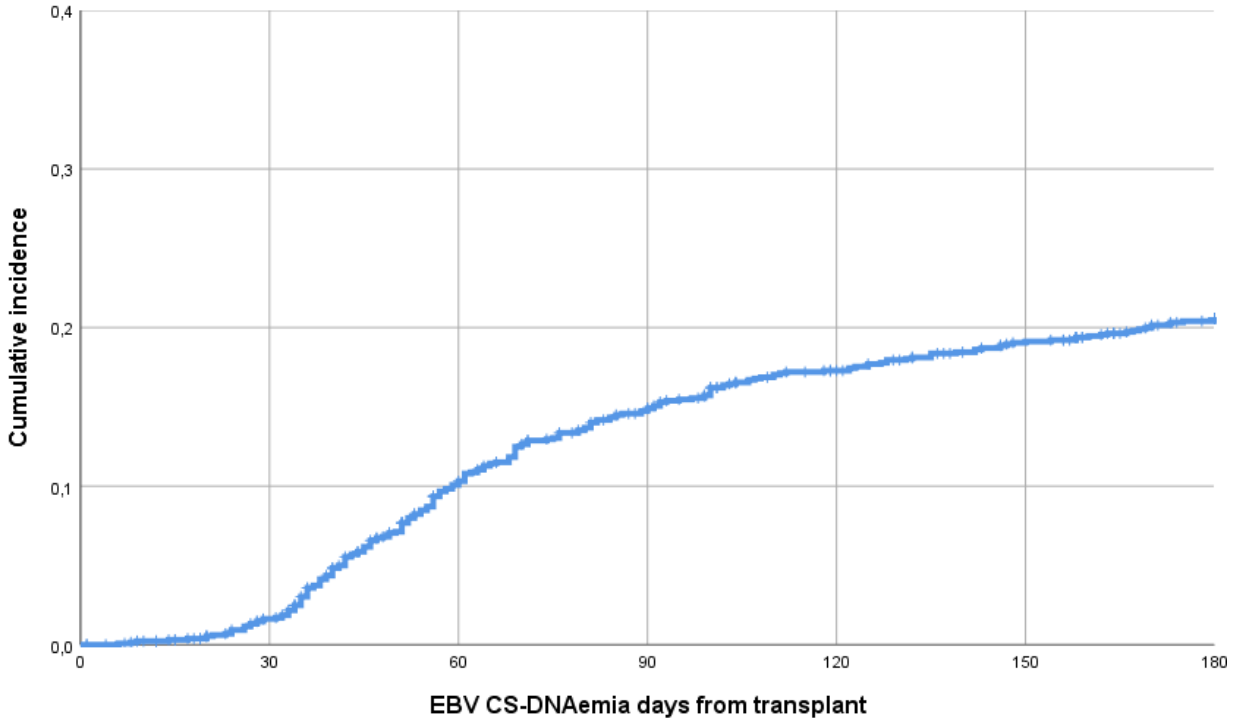
Abbreviations: EBV, Epstein-Barr virus; HCT, hematopoietic cell transplanation; IVIG, intravenous immunoglobulin; PTLD, post-transplant lymphoproliferative disorder, SOT, solid organ transplantation; VSTs, virus-specific T cells.

[a]Grading recommendations for SOT: (x/y); x = strength of recommendation; y = quality of evidence.

[b]Grading recommendations for HCT: A = strong; B = moderate; C = marginal; D = against; I = at least 1 RCT; II = at least from one clinical trial; III = expert opinion, descriptive studies.

A PROSPECTIVE, MULTICENTER SURVEY OF HUMAN CYTOMEGALOVIRUS (CMV) AND OTHER HERPESVIRUSES INFECTIONS AND DISEASES IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (ALLO-HSCT) RECIPIENTS.
CLINICALTRIALS.GOV IDENTIFIER: NCT04412811

Cumulative incidence of clinically significant EBV DNAemia in allo-HSCT



20.6%

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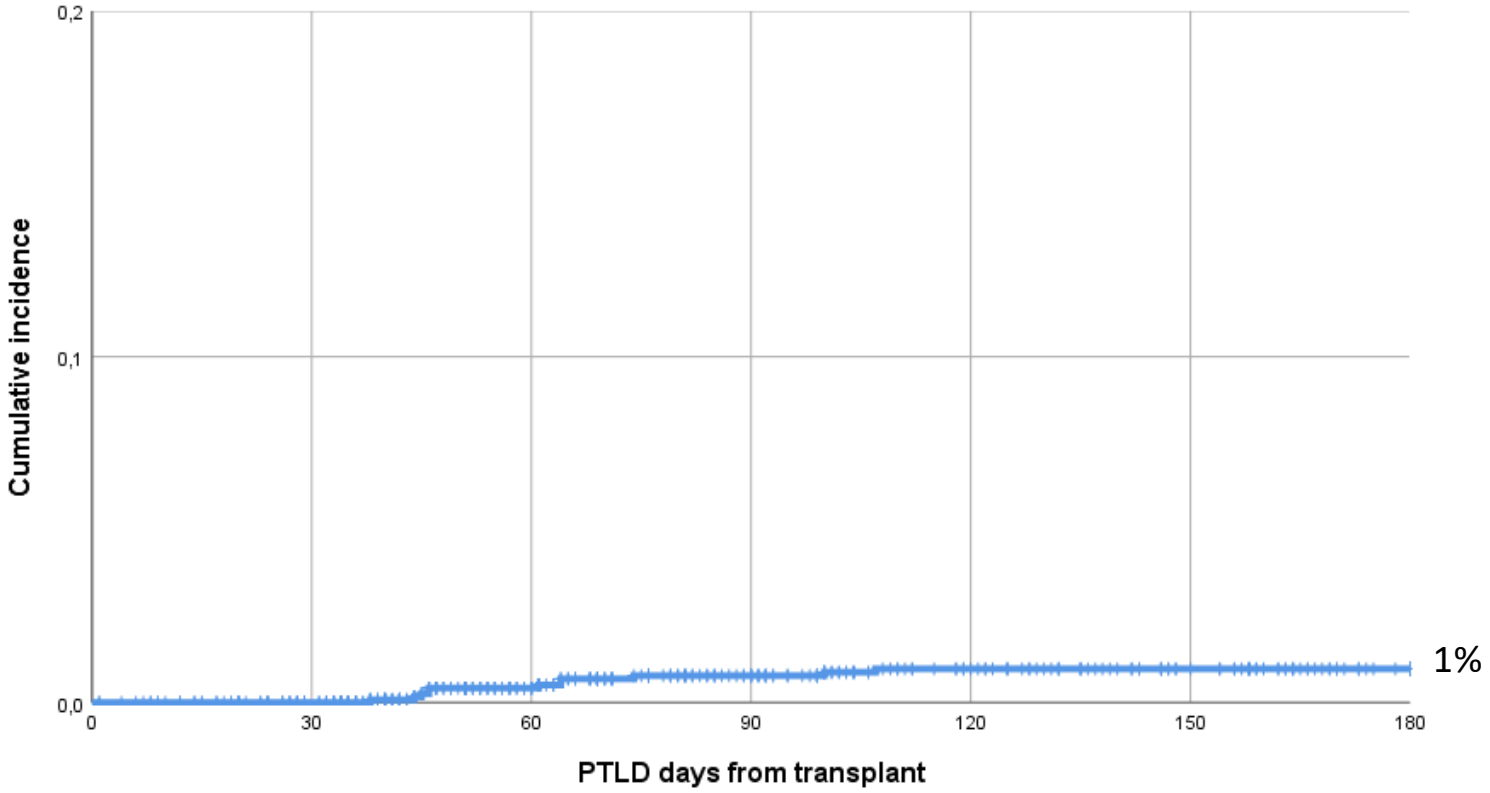
Cumulative incidence of PTLD in allo-HSCT



1%

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CLINICALTRIALS.GOV IDENTIFIER: NCT04412811

Risk of CS-EBV DNAemia: variables considered in the analysis

- Age
- Sex
- Underlying disease: AL vs other
- Disease phase: CR, chronic, noCR
- Previous allo-HSCT
- Type of donor
- Conditioning regimen
- Stem cell source
- Letermovir prophylaxis

- T-cell depletion, ATG
- PT-CY
- R/D CMV serology
- ECOG PS
- HCT-CI
- Time of engraftment
- A-GVHD
- CS-CMV DNAemia

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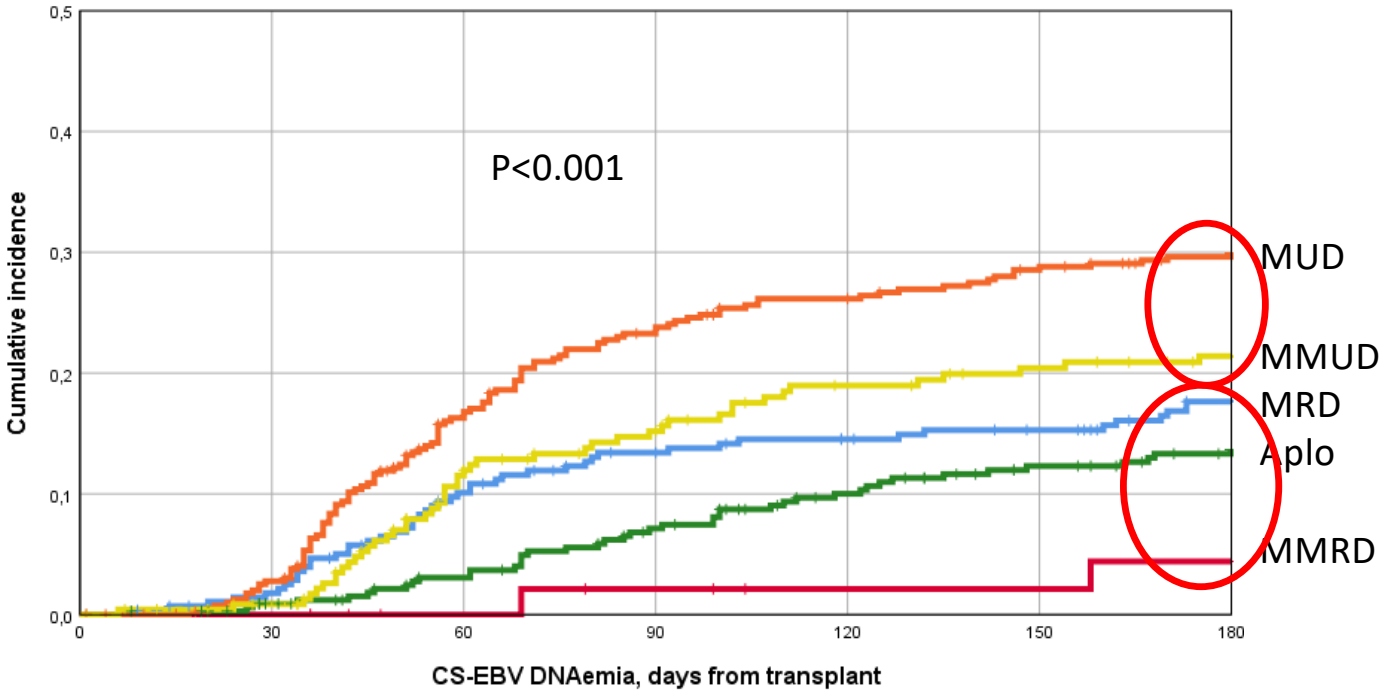
Risk of CS-EBV DNAemia: type of transplant



PTLD: 11 cases

- MUD: 7 cases
- MMUD:2 cases
- MRD: 1 case
- Aplo: 1 case

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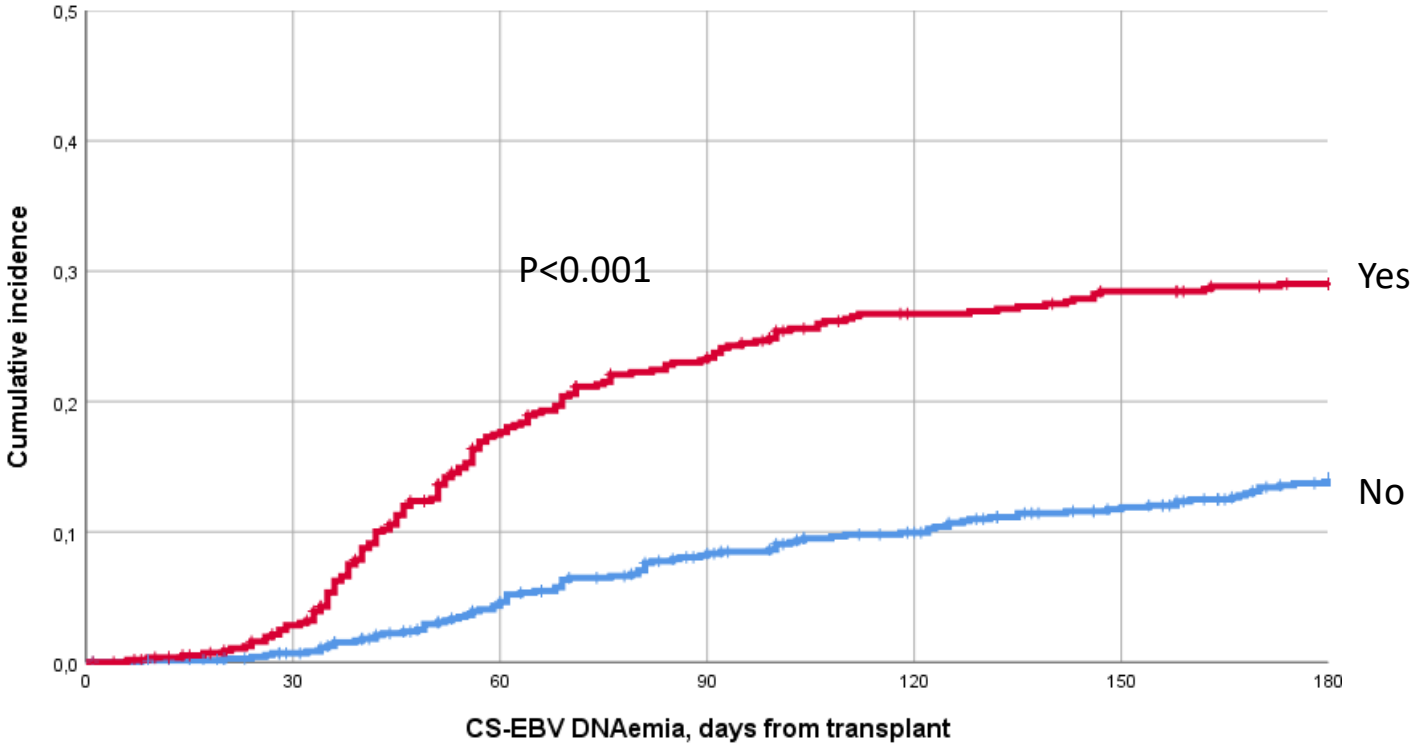
CLINICALTRIALS.GOV IDENTIFIER: NCT04412811

Risk of CS-EBV DNAemia: T cell depletion (ATG)



PTLD: 11 cases

- TCD: 9 cases
- No TCD:2 cases

A PROSPECTIVE, MULTICENTER SURVEY OF HUMAN CYTOMEGALOVIRUS (CMV) AND OTHER HERPESVIRUSES INFECTIONS AND DISEASES IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (ALLO-HSCT) RECIPIENTS.
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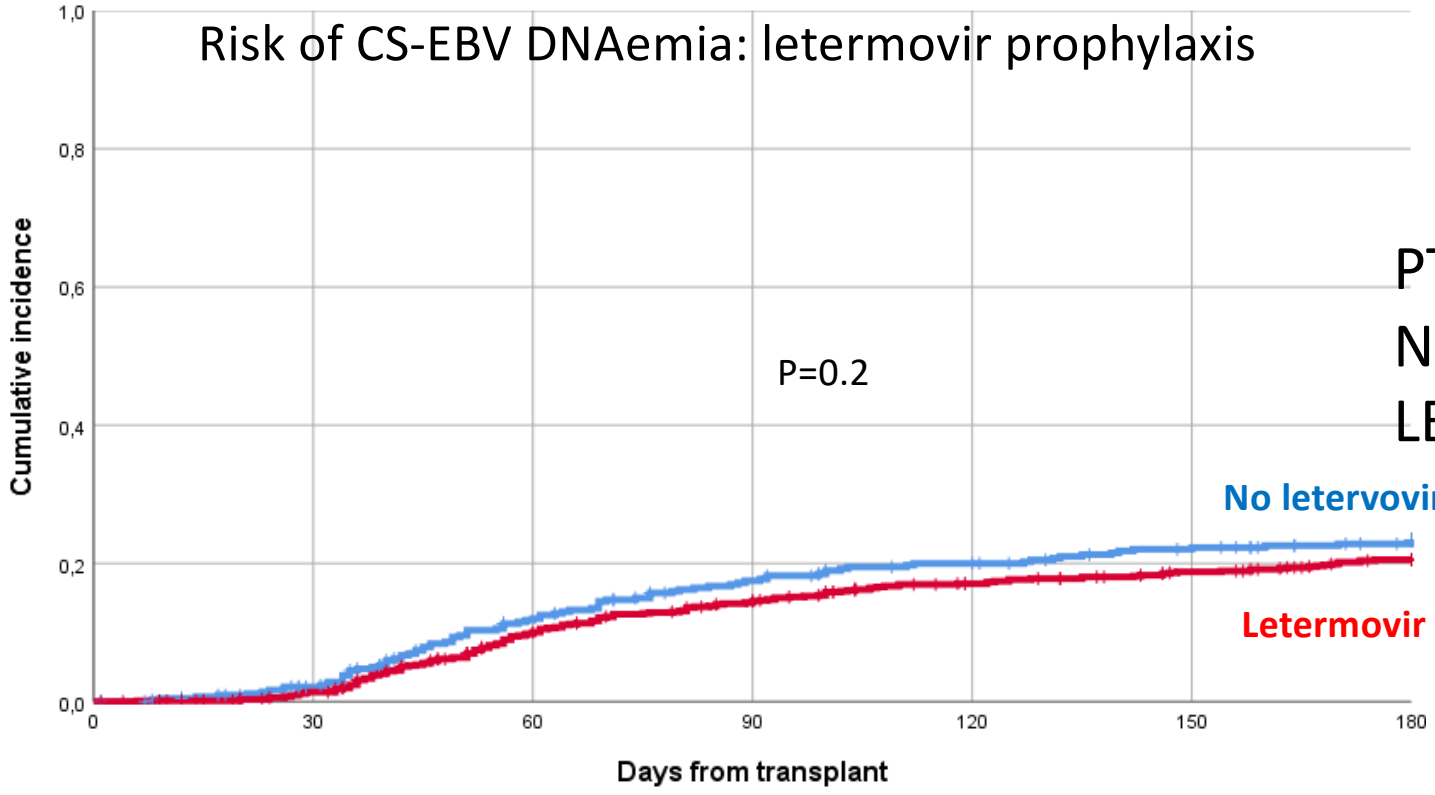

PTLD: 11 cases
No-LET: 3 case
LET: 8 cases

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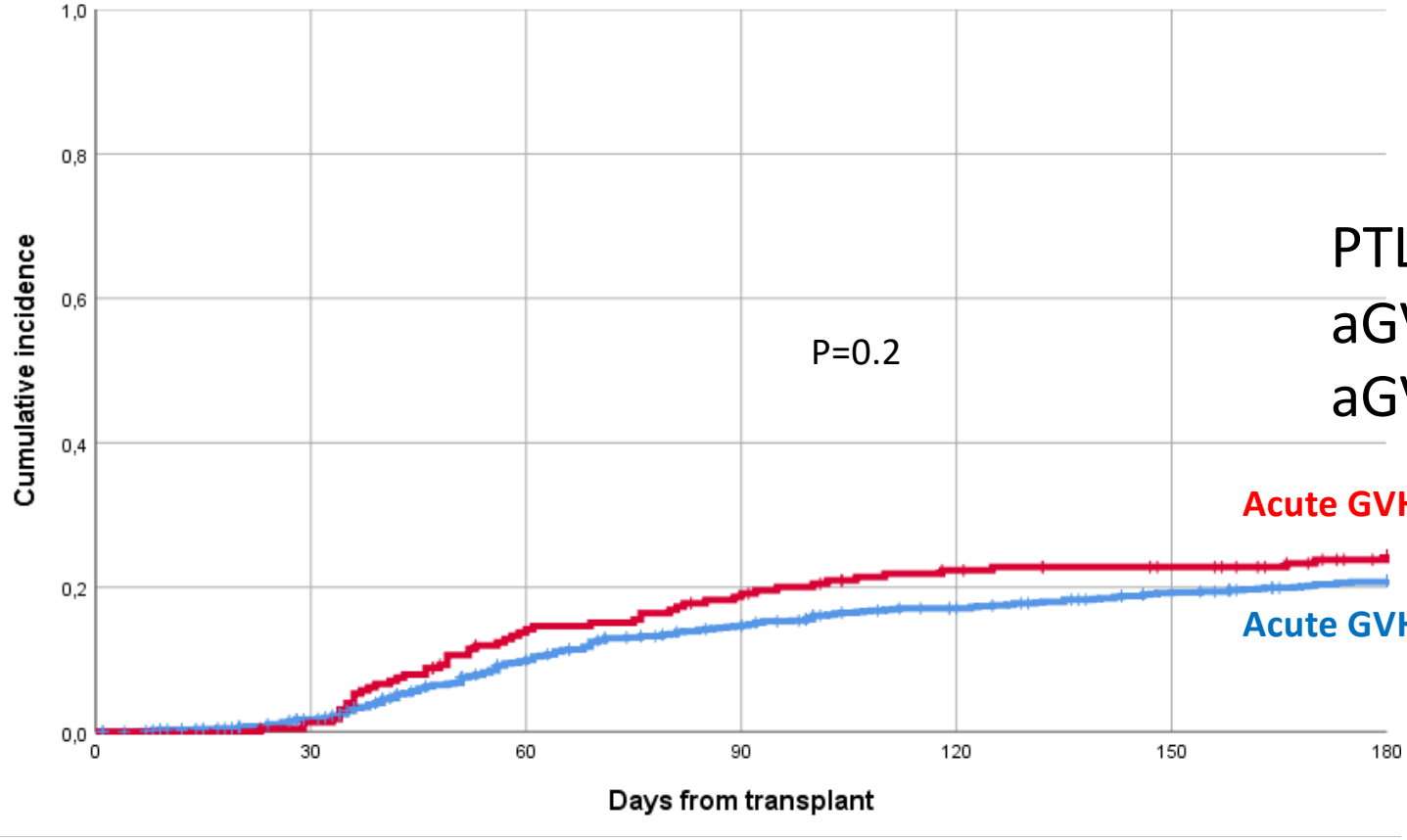
Risk of CS-EBV DNAemia: acute GVHD



PTLD: 11 cases
aGVHD, 0-1: 10 cases
aGVHD, 2-4: 1 case

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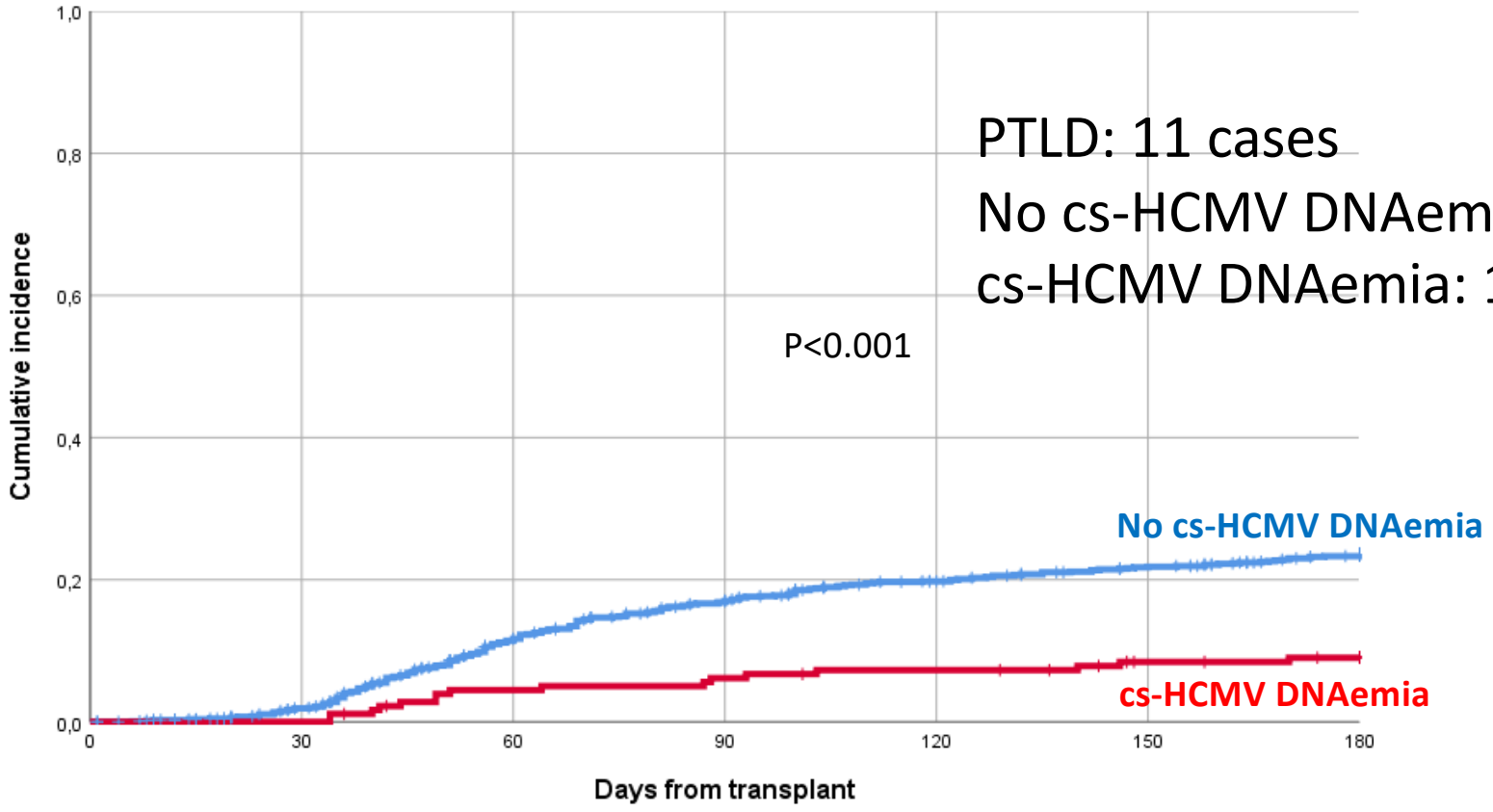
Risk of CS-EBV DNAemia: HCMV cs-DNAemia



PTLD: 11 cases
No cs-HCMV DNAemia: 10 cases
cs-HCMV DNAemia: 1 case

A PROSPECTIVE, MULTICENTER SURVEY OF HUMAN CYTOMEGALOVIRUS (CMV) AND OTHER HERPESVIRUSES INFECTIONS AND DISEASES IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (ALLO-HSCT) RECIPIENTS.
CLINICALTRIALS.GOV IDENTIFIER: NCT04412811

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Risk of CS-HCMV DNAemia, no letermovir

Variables		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p	HR (95% CI)	p
Gender	Female	1.00			
	Male	1.02 (0.63-1.66)	0.93		
Age (increased by 10 years)		0.97 (0.96-0.98)	<0.001		
Age	<18 years	1.00			
	>= 18 years	0.22 (0.13-0.35)	<0.001	0.25 (0.15-0.42)	<0.001
Underlying hematologic disease	Diseases other than acute leukemia	1.00			
	Acute leukemia	0.67 (0.42-1.06)	0.085		
Phase of the underlying disease at transplant	Complete remission	1.00			
	Chronic phase	1.50 (0.83-2.69)	0.18		
	No complete remission	2.14 (1.22-3.77)	0.008		
Previous HSCT	No	1.00			
	Previous auto-HSCT	0.76 (0.25-2.33)	0.64		
	Previous allo-HSCT	1.74 (0.75-4.06)	0.20		
CS-HCMV Infection in the 3 months before transplant	No	1.00			
	Yes	3.68 (1.00-13.6)	0.051		
Recipient/donor HCMV serology	Negative/negative	1.00			
	Negative/positive	7.82 (0.97-62.8)	0.053	7.80 (1.00-61.1)	0.050
	Positive/Negative	33.1 (4.45-246)	<0.001	31.5(4.31-229)	<0.001
	Positive/Positive	34.1 (4.75-245)	<0.001	21.9 (3.06-157)	0.002
ECOG performance status at transplant	0-1	1.00			
	>1	0.66 (0.21-2.05)	0.47		
HCT comorbidity index at transplant	Score 0	1.00			
	Score 1-2	0.65 (0.36-1.18)	0.16		
	Score >=3	0.39 (0.17-0.89)	0.026		
Stem Cell Source	Peripheral blood	1.00			
	Bone marrow	1.68 (1.04-2.71)	0.033		
	Cord blood	0.96 (0.15- 6.20)	0.97		

Variables		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p	HR (95% CI)	p
Donor type	Matched related	1.00			
	Mismatched related	1.86 (0.71-4.90)	0.21		
	Haploidentical	1.59 (0.84-3.01)	0.15		
	Matched unrelated	1.07 (0.56- 2.06)	0.84		
	Mismatched unrelated	0.74 (0.31- 1.78)	0.50		
Conditioning regimen	Myeloablative	1.00			
	Non myeloablative/ reduced intensity	0.81 (0.47-1.40)	0.46		
T cell depletion	No	1.00			
	Yes	1.38 (0.87-2.21)	0.18		
Use of post transplant cyclophosphamide as GVHD prophylaxis	No	1.00			
	Yes	1.25 (0.75-2.09)	0.40		
Days to engraftment	<=20 days	1.00			
	>20 days	1.11 (0.68-1.84)	0.67		
Prophylaxis with CMV specific immunoglobulins	No	1.00			
	Yes	0.47 (0.12-1.91)	0.29		
Acute GvHD *	Grade 0-I	1.00			
	Grade II-IV	1.43 (0.81-2.52)	0.22		
EBV DNAemia*	Negative or <1000 copies/ml	1.00			
	>=1000 copies /ml	0.33 (0.15-0.75)	0.009	0.27 (0.11-0.62)	0.002
Gram negative * bacteremia	No	1.00			
	Yes	0.81 (0.41-1.61)	0.55		
Invasive fungal disease *	No	1.00			
	Yes	0.34 (0.52-3.49)	0.55		

* only cases observed before CS-HCMV infection were considered

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GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

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Has EBV a protective role against CS-HCMV-i in patients who do not receive LET-PP?

An immunological response to EBV infection may somehow interfere with HCMV reactivation.

- **EBV is a polyclonal stimulator**
- **EBV levels and B-cell reconstitution were prospectively monitored in a cohort of allo-HSCT patients (Burns, Blood 2015). In patients with low or undetectable levels of EBV, the circulating B-cell pool consisted predominantly of transitional and naive cells, with a marked deficiency of CD27+ memory cells. On the contrary, among patients with high EBV loads, there was a significant increase in both the proportion and number of CD27+ memory B cells.**
- **Some murine model studies showed that memory B cells can mediate protection against CMV in the absence of T cell help and transfer of memory B cells may be effective in protecting from an already ongoing viral infection (Winkler ,Blood 2006; Klenovsek 2007).**