2nd European Conference on Infections in Leukemia

Recommendations for EBV management in patients with leukemia

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ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Society for Oncology and Immunocompromised Host

Citations in PubMed: EBV + leukemia

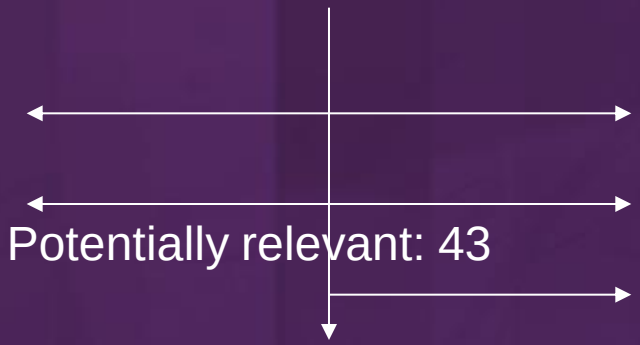
Total	= 1822
Meta-analysis	= 0
Randomized CT	= 4 (no relevance)
Practice guidelines	= 0
Case reports	= 356
Reviews	= 246
Comparative studies	= 153
Multicenter studies	= 7
Letters	= 41

Citations in PubMed: EBV + leukemia + therapy

Total articles retrieved: 450

RCT: 0

Meta-analyses: 0



Reviews: 95

Case reports: 158

Letters: 22

Potentially relevant: 43

+Abstracts from the proposed meetings: ~60

Definitions

EBV biology

Type of infection:

1. Primary (early) – in children and adolescents (e.g. infectious mononucleosis)
2. Latent (late) – reactivation in immunocompromised patients

Most EBV reactivations are subclinical and require no therapy.

Clinical syndromes associated with EBV infection

Primary syndromes:

1) Infectious mononucleosis
2) Chronic active EBV infection
3) X-linked lymphoproliferative syndrome

EBV-associated tumors (reactivation syndromes):

4) Lympho-proliferative disorders (LPD) in immunocompromised patients
5) Burkitts Lymphoma / NHL
6) Naso-pharyngeal carcinoma
7) NK leukemia
8) HD (de novo and post allo-HSCT)
9) Hemophagocytic lymphohistiocytosis
10) Angioblastic T-cell lymphoma

EBV-associated post-transplant diseases:

11) Encephalitis / myelitis
12) Pneumonia
13) Hepatitis

Definitions – diagnosis (1)

- Primary EBV infection
  - EBV occurring in a previously EBV seronegative patient (after primary infection, EBV is constantly replicating, with or without detected viral load)

<u>All other definitions are related to late (latent) infection</u>

- EBV-DNA-emia (previously: EBV reactivation)
  - Detection or rise in EBV load in the blood in the seropositive patient +/- symptoms (fever with or without other symptoms) with no sign of EBV endorgan disease

Definitions – diagnosis (2)

- **Probable EBV disease**
  - **Significant lymphadenopathy, hepatosplenomegaly, or organ manifestations without documented underlying pathophysiology with high EBV blood load (without biopsy)**

- **Proven EBV disease (PTLD or other endorgan disease)**
  - **EBV detected from an organ by biopsy or other invasive procedures with a test with appropriate sensitivity and specificity together with symptoms and/or signs from the affected organ**

Definitions – diagnosis (3)

- **Post-Transplant Lymphoproliferative Disorder (PTLD)**
  - **Heterogenous group of EBV diseases with neoplastic lymphoproliferation, developing after transplantation and caused by iatrogenic suppression of T-cell function**

Diagnosis of neoplastic forms of EBV-PTLD should have at least two of the following histological features:

1. Disruption of underlying cellular architecture by a lymphoproliferative process

2. Presence of monoclonal or oligoclonal cell populations as revealed by cellular and/or viral markers

3. Evidence of EBV infection in many of the cells i.e. DNA, RNA or protein.

Detection of EBV nucleic acid in blood is not sufficient for the diagnosis of EBV-related PTLD. **(EBMT IDWP definitions, 2007)**

Definitions – therapy (4)

- Prophylaxis of EBV-DNA-emia (EBV reactivation)
  - Any agents given to an asymptomatic patient to prevent EBV reactivation in seropositive patient (or when the donor is seropositive)
- Preemptive therapy (when EBV reactivation is diagnosed)
  - Any agents or EBV-specific T-cells given to an asymptomatic patient with EBV detected by a screening assay
- Treatment of EBV disease
  - Agents or other therapeutic methods applied to a patient with EBV (proven or probable) disease

Risk factors of PTLD

High risk HSCT for PTLD development = allogeneic HSCT with the following risk factors:

- unrelated /mismatch HSCT
- T-cell depletion or ATG / OKT3 use
- EBV serology mismatch
- primary EBV infection
- splenectomy

The risk increases with the number of risk factors

Epidemiology

Incidence of EBV-LPS after SCT

	Camp ath	Auto-Tx	MSD HSCT	MSD HSCT	BMT MM SD	Haplo	UCBT	UD-HSCT	TCD MUD	TCD MUD
Incidence	**1.3%**	**0.07%**	**0.4%**	**0%**	**1.4%**	**25%**	**4.5%**	**4%**	**29%**	**11.7%**
n	1641	1350	1868	226	368	12	335	320	65	85
Source	Hale 1998	Penike t 1998	Zutter 1988	Sundin 2006	Zutter 1988	Comoli 2007	Brunstein 2006	Sundin 2006	Geritsen 1996	Van Esser 2001

Prevention of EBV reactivation

Allogeneic stem cell transplantation (1)

- EBV reactivations are common after SCT and rarely cause significant problems through direct viral end-organ disease. The important complication of EBV infection is post-transplant lymphoproliferative disease (PTLD).

- The prevention of PTLD is still of major importance in allogeneic HSCT patients at high risk, since the outcome of PTLD is very poor.

- SCT patients should be tested for EBV serology (AII). If a patient is found to be seronegative, the risk of PTLD is higher when the donor is positive.

- When there is a choice, the selection of seronegative donor might be beneficial, since EBV might be transmitted with the graft (BII).

- SCT donors should be tested before transplantation for EBV serology, particularly in unrelated or mismatched donors, or when ATG use or T-depletion is planned (AII)

Allogeneic stem cell transplantation (2)

- After high-risk allo-HSCT, prospective monitoring of EBV-viremia is recommended (BII).

- High risk patients after allo-HSCT should be closely monitored for symptoms or signs attributable to EBV and PTLD (BII).

- Immune globulin for prevention of EBV reactivation or disease is not recommended (DIII).

- The risk in HLA-identical sibling transplant recipients not receiving T-cell depletion is low and no routine screening for EBV is recommended (DII).

Patients with hematological malignancies including autologous SCT recipients

- EBV infection is of minor importance in patients on standard chemotherapy.
- It is not recommended that autologous transplant patients be routinely monitored for EBV before and after HSCT (DIII).
- It is not recommended that conventional chemotherapy patients be routinely monitored for EBV (DIII).

Diagnosis of EBV reactivation

Diagnosis of EBV reactivation - techniques

- Prospective monitoring of EBV-viremia by PCR is recommended after high-risk allo-HSCT (BII)

- Material: Different materials were used and currently there is no data to select the best one. However, it is not recommended to test EBV load in PBL (peripheral blood lymphocytes) (DIII)

Diagnosis of EBV reactivation

- Beginning of monitoring: day of HSCT (although PTLD rarely occurs in first month after HSCT)

- Frequency:

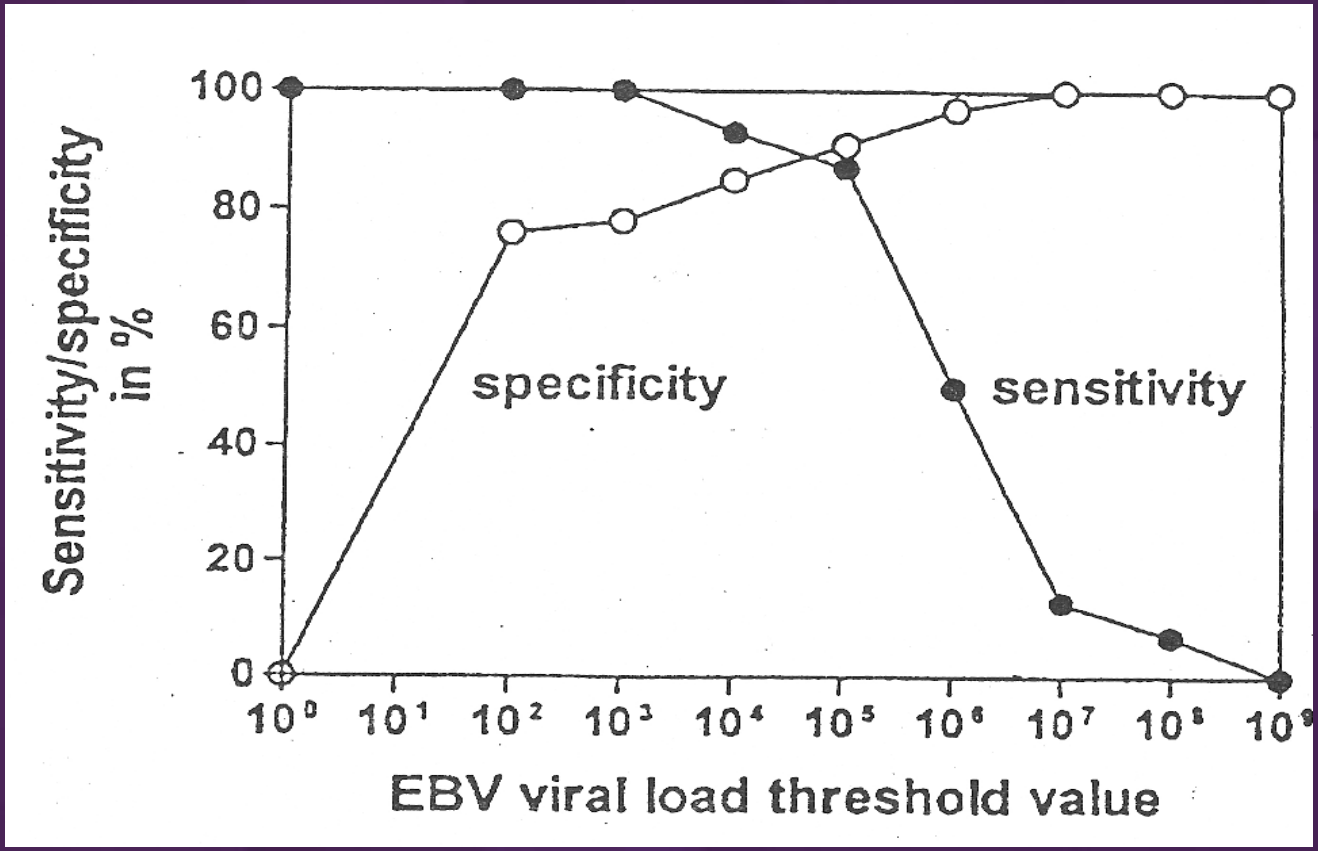
  - screening (in EBV-negative pts) testing is recommended once a week (BII)

  - in patients with rising EBV DNA more frequent sampling might be considered (CII)

- End of screening: 3 months in high risk patients; longer screening/monitoring is recommended in patients with GVHD or after haplo-HSCT or in those having experienced an earlier EBV reactivation (BII).

- Strategy might depend on individual assessment of patient.

Threshold value calculation for EBV load for diagnosis of PTLD in HSCT patients



The corresponding sensitivities and specifities for different threshold values

From Gärtner et al, 2002

Diagnosis of EBV disease

Diagnosis of PTLD

- Diagnosis of PTLD must be based on symptoms and/or signs consistent with PTLD together with detection of EBV by an appropriate method applied to a specimen from the involved tissue (AII).

- Definitive diagnosis of EBV-PTLD requires: biopsy and histological examination (including immunohistochemistry or flow cytometry for CD19+ and CD20+).

- EBV detection requires: detection of viral antigens or in situ hybridization for the EBER transcripts (AII).

Prophylaxis of EBV reactivation

Prophylaxis in allo-SCT recipients

Data are contradictory; low number of patients.

Although antiviral drugs can inhibit replication, there is no data that they have any impact on the development of EBV-PTLD. Antiviral drugs are not recommended (EII).

IGIV has no impact in EBV prophylaxis (DIII)

Routine anti-EBV antiviral prophylaxis is not recommended in patients with other hematological malignancies (EIII)

Preemptive therapy

Preemptive therapy for EBV-PTLD after HSCT

1. Rituximab, 375 mg/m^2, 1-2 doses (AII)
2. Reduction of immunosuppressive therapy, if possible (BII)
3. Donor EBV-specific CTL (cytotoxic T cell therapy) infusion (if available) (CII)

Antiviral drugs are not recommended for preemptive therapy (EII).

Problem: Down-regulation of CD20 expression on lymphoma cells following repeated therapy with anti-CD20 MoAb's, causing refractoriness to rituximab.

Response to preemptive therapy

The response to therapy could be identified by a decrease in EBV-DNA load of at least 1 log of magnitude in the first week of treatment (BIII).

Treatment of PTLD

Therapy in PTLD – first line

1. Anti-CD20 monoclonal antibodies (Rituximab) (AII)
2. Reduction of immunosuppressive therapy, if possible (BII)
3. Adoptive immunotherapy with *in vitro* generated EBV-cytotoxic T-cells, if available (BII)

   - Allogeneic EBV-specific cytotoxic T lymphocytes (CTL) . Number of EBV-CTL doses: 2-4.

   - Autologous EBV-specific cytotoxic T lymphocytes are optional (CIII)

4. DLI in order to restore T-cell reactivity (CIII)

Therapy in PTLD – second line

1. Chemotherapy is a potential option for PTLD therapy after failure of other methods (CII)
2. IGIV have no impact in PTLD (DIII)
3. Antiviral agents are not recommended for PTLD therapy (EII)

Summary of available publications on EBV therapy (related to leukemia and HSCT pts)

METHOD	SOURCE	PTS	CURE	IMPROVEMENT	DEATH
Rituximab Preemptive	33 papers	133	111 (83%)	12	10
Rituximab PTLD	14 papers	43	38 (88%)		5
CTL	8 papers	74	73 (98%)		1

Summary of available EBMT and ASH abstracts on EBV therapy

(related to leukemia and HSCT patients)

METHOD	# abstracts	PTS	CURE	IMPROVEMENT	DEATH
Rituximab Preemptive	13	110	93 (84%)	6	6
Rituximab PTLD/EBV dis.	6	33	18 (47%)	9	7
Rituximab prophylactically	2	23	14 (61%)	9	
CTL	1	4	4 (100%)		

2 abstracts with large number of patients are excluded due to ambiguous data

EBV infections: ECIL recommendations

DIAGNOSIS	Chemotherapy Auto-HSCT	High-risk Allo-HSCT		GVHD, haplo, early EBV reactivation
		Before	After	
Serology	DIII	AII		
EBV-DNA	DIII		BII	BII
Preemptive			AII	AII

EBV infections: ECIL recommendations

	EBV-DNA-emia (=EBV reactivation)	EBV disease (probable/proven)
THERAPY	Preemptive therapy	EBV therapy
RITUXIMAB	AII	AII
REDUCTION IST	BII	BII
EBV-CTL	CII	CII
OTHER	DLI CIII	CHEMO CII
ANTIVIRALS	EII	EII

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