2011 Update on the ECIL-3 guidelines for EBV management in patients with leukemia and other hematological disorders

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Definitions

EBV biology

Type of infection:

1. Primary (first) – in children and adolescents (e.g. infectious mononucleosis)
2. Recurrent – reactivation in immunocompromised patients

Most EBV primary and recurrent infections 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
4) Hemophagocytic lymphohistiocytosis (HLH)

EBV-associated tumors:

5) Post transplant lympho-proliferative disorders (PTLD) in immunocompromised patients
6) Burkitts Lymphoma / NHL
7) Naso-pharyngeal carcinoma
8) T/NK lymphomas
9) HD (de novo and post allo-HSCT)
10) Angioblastic T-cell lymphoma

EBV-associated post-transplant diseases:

11) Encephalitis / myelitis
12) Pneumonia
13) Hepatitis

Definitions – diagnosis (1)

- **Primary EBV infection**
  - EBV detected (nucleic acid or serologically) in a previously EBV seronegative patient

- **EBV-DNA-emia**
  - detection of EBV DNA in the blood

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 disease**
  - **Any agents given to an asymptomatic patient to prevent EBV DNA-emia in seropositive patient (or when the donor is seropositive)**

- **Preemptive therapy for EBV disease**
  - **Any agents or EBV-specific T-cells given to an asymptomatic patient with EBV DNA-emia**

- **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:

Major:
- **unrelated / mismatch HSCT**
- **T-cell depletion (in vivo or in vitro)**
- **EBV serology mismatch**
- **cord blood HSCT**

Minor:
- **primary EBV infection**
- **splenectomy**
- **chronic GVHD**

The risk increases with the number of risk factors

Prevention of EBV disease

Allogeneic stem cell transplantation (1)

- **EBV DNA-emia is common after HSCT 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 poor.**

- **HSCT patients should be tested for EBV antibodies. The recommendation is stronger in pediatric patients (AII) than in adults (BII). 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).**

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

Allogeneic stem cell transplantation (2)

- **All transplant candidates, particularly those who are EBV-seronegative, should be advised of behaviors that would decrease the likelihood of EBV exposure (AII)**
- **After high-risk allo-HSCT, prospective quantitative monitoring of EBV DNA-emia is recommended (AII).**
- **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 DNA-emia or disease is not recommended (BIII).**
- **The risk in HLA-identical sibling transplant recipients not receiving T-cell depletion is low and no routine screening for EBV is recommended (BII).**

Patients with hematological malignancies including autologous HSCT 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 (BIII).**
- **It is not recommended that conventional chemotherapy patients be routinely monitored for EBV (BIII).**

Diagnosis of EBV DNA-emia

Diagnosis of EBV DNA-emia - techniques

- Prospective quantitative monitoring of EBV DNA by PCR is recommended after high-risk allo-HSCT (AII)

- Material: whole blood, plasma, serum (BIII)

Diagnosis of EBV DNA-emia

- **Start to monitor: day of HSCT**

- **Frequency:**

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

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

- **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.**

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 disease

Prophylaxis in allo-SCT recipients

- **B-cell depletion might reduce the risk of EBV-PTLD (CII)**
- **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 (BII).**
- **IGIV is not recommended for EBV prophylaxis (BIII)**
- **Routine anti-EBV antiviral prophylaxis is not recommended in patients with other hematological malignancies (AIII)**

Preemptive therapy against EBV disease

Preemptive therapy for EBV-DNA-emia after HSCT

1. **Anti-CD20 MoAb's (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 (if available) (CII)**

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

Response to preemptive therapy

The response to therapy could be identified by a decrease in EBV DNA-emia 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 (AII)**

Therapy in PTLD: second line

1. **Chemotherapy is a potential option for PTLD therapy after failure of other methods (CII)**
2. **Adoptive immunotherapy with *in vitro* generated CTL, if available (CII)**

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

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

Therapy in PTLD: third line

1. **DLI in order to restore T-cell reactivity (CIII)**
2. **IGIV is not recommended for PTLD (BIII)**
3. **Antiviral agents are not recommended for PTLD therapy (AII)**

EBV infections: ECIL recommendations

DIAGNOSIS	Chemotherapy Auto-HSCT	High-risk Allo-HSCT	
		Before	After
Serology	NO - BIII	YES - AII	
EBV-DNA	NO - BIII		YES - AII
Preemptive therapy			YES - AII

EBV infections: ECIL recommendations

THERAPY	EBV-DNA-emia (high or rising) Preemptive therapy	EBV disease (probable/proven) EBV therapy
RITUXIMAB	YES - AII	YES - AII
REDUCTION IST	YES - AII	YES - AII
EBV-CTL	YES - CII	YES - CII
OTHER	YES: DLI CIII	CHEMO CII DLI CIII
ANTIVIRALS	NO - AII	NO - AII