EBV in HSCT
2015 update of ECIL guidelines

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INTRODUCTION

• First recommendations for management of EBV infections in patients undergoing HSCT or treated for hematological malignancies - at ECIL-2 (Styczynski et al., BMT, 2009), updated at ECIL-3

• Goals for 2015 update:
  ✓ To update the recommendations with analysis of the new data
  ✓ To change previous 5-grade scale (A to E) into a 4-grade scale (A to D) for Strength of Recommendations and adding index for source of level II in Quality of Evidence (I to III)

All ECIL6 changes appear in red on the next slides
### GRADING SCALE

#### STRENGTH OF RECOMMENDATION (SoR)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ECIL strongly supports a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>ECIL moderately supports a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>ECIL marginally supports a recommendation for use</td>
</tr>
<tr>
<td>D</td>
<td>ECIL supports a recommendation against use</td>
</tr>
</tbody>
</table>

#### QUALITY OF EVIDENCE (QoE)

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least 1 properly designed randomized, controlled trial (orientated on the primary endpoint of the trial)</td>
</tr>
<tr>
<td>II*</td>
<td>Evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from &gt; 1 centre); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees</td>
</tr>
</tbody>
</table>

#### ADDED INDEX FOR SOURCE OF LEVEL II EVIDENCE

<table>
<thead>
<tr>
<th>*Index</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>Meta-analysis or systematic review of RCT</td>
</tr>
<tr>
<td>t</td>
<td>Transferred evidence, that is, results from different patients’cohorts, or similar immune-status situation</td>
</tr>
<tr>
<td>h</td>
<td>Comparator group: historical control</td>
</tr>
<tr>
<td>u</td>
<td>Uncontrolled trials</td>
</tr>
<tr>
<td>a</td>
<td>Published abstract presented at an international symposium or meeting</td>
</tr>
</tbody>
</table>
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) Lymphoproliferative disorders (LPD) in immunocompromised patients
6) Burkitt Lymphoma
7) EBV-positive DLBCL of the elderly
8) Naso-pharyngeal carcinoma
9) T/NK lymphomas
10) Hodgkin lymphoma (de novo and post allo-HSCT)
11) Angioimmunoblastic T-cell lymphoma

EBV-associated post-transplant diseases
12) PTLD: post-transplant lymphoproliferative disorder
13) Hemophagocytic lymphohistiocytosis (HLH)
14) Other rare end-organ diseases: encephalitis, myelitis, hepatitis, pneumonia
15) Oral hairy leukoplakia
DEFINITIONS – DIAGNOSIS (1)

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

- **Recurrent EBV infection**
  - detection of EBV DNA in the blood in an EBV-seropositive patient
DEFINITIONS – DIAGNOSIS (2)

• **Probable EBV disease**
  – Significant lymphadenopathy, hepatosplenomegaly, or other end-organ manifestations (without tissue biopsy, but in the absence of documented underlying pathophysiology) together with significant EBV DNAemia

• **Proven EBV disease (PTLD or other endorgan disease)**
  – Detection of EBV nucleic acids or EBV-encoded proteins in a tissue specimen, together with symptoms and/or signs from the affected organ
DEFINITIONS – DIAGNOSIS (3)

• Post-Transplant Lymphoproliferative Disorder (PTLD)
  – Heterogeneous group of neoplastic lymphoproliferations, developing after transplantation as a consequence of iatrogenic suppression of T-cell numbers and/or function; can be EBV related or not.
  – EBV+PTLD = proven EBV disease (by definition)

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

• Prophylaxis
  – Any agent given to **EBV-seropositive** patient to prevent EBV DNA-emia

• Preemptive therapy
  – **Drug or cellular therapy** given to a patient with EBV DNA-emia **to prevent EBV disease**

• Treatment of EBV disease / PTLD
  – **Therapeutic interventions** for patients with probable or proven EBV disease
EPIDEMIOLOGY
# INCIDENCE OF EBV DNA-emia after HSCT

<table>
<thead>
<tr>
<th>Type of HSCT</th>
<th>INCIDENCE</th>
<th>N</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSD/MUD/MMUD</td>
<td>3%</td>
<td>854</td>
<td>Ocheni 2008</td>
</tr>
<tr>
<td>MSD/MUD/MMUD</td>
<td>52.9% at 3m</td>
<td>70</td>
<td>Worth 2011</td>
</tr>
<tr>
<td>MSD/MUD-HSCT (HR)</td>
<td>29.4% at 1y</td>
<td>133</td>
<td>Garcia-Cardenas 2015</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>63% at 100d</td>
<td>89</td>
<td>Cesaro 2010</td>
</tr>
<tr>
<td>Haplo (TCD)</td>
<td>44.4%</td>
<td>27</td>
<td>Comoli 2007</td>
</tr>
<tr>
<td>Haplo (PTCy)</td>
<td>0.1%</td>
<td>762</td>
<td>Kanakry 2013</td>
</tr>
<tr>
<td>CBT</td>
<td>5% at 3y</td>
<td>288</td>
<td>Sanz 2014</td>
</tr>
<tr>
<td>CBT</td>
<td>13.7% at 1y</td>
<td>175</td>
<td>Dumas 2013</td>
</tr>
<tr>
<td>RIC-CBT</td>
<td>17% at 2y</td>
<td>33</td>
<td>Peric 2012</td>
</tr>
<tr>
<td>Alemtuzumab (HSCT)</td>
<td>40.3% at 2y</td>
<td>111</td>
<td>Carpenter 2010</td>
</tr>
</tbody>
</table>
## INCIDENCE OF EBV-PTLD AFTER HSCT

<table>
<thead>
<tr>
<th>Type of HSCT</th>
<th>INCIDENCE</th>
<th>N</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSD-HSCT</td>
<td>1.16%</td>
<td>1902</td>
<td>Styczynski 2013</td>
</tr>
<tr>
<td>MMFD / Haplo (TCD)</td>
<td>2.86%</td>
<td>455</td>
<td>Styczynski 2013</td>
</tr>
<tr>
<td>Haplo (PTCy)</td>
<td>0%</td>
<td>762</td>
<td>Kanakry 2013</td>
</tr>
<tr>
<td>MUD</td>
<td>3.97%</td>
<td>1762</td>
<td>Styczynski 2013</td>
</tr>
<tr>
<td>MMUD</td>
<td>11.24%</td>
<td>347</td>
<td>Styczynski 2013</td>
</tr>
<tr>
<td>CBT</td>
<td>4.06%</td>
<td>345</td>
<td>Styczynski 2013</td>
</tr>
<tr>
<td>CBT (RIC)</td>
<td>12.9%</td>
<td>47</td>
<td>Sanz 2014</td>
</tr>
<tr>
<td>Auto-HSCT (no TCD)</td>
<td>7 ped cases only reported in literature</td>
<td></td>
<td>Eckrich 2012</td>
</tr>
<tr>
<td>Auto-HSCT (TCD)</td>
<td>3.5%</td>
<td>212</td>
<td>Nash 2003, Powell 2004</td>
</tr>
<tr>
<td>Alemtuzumab (HSCT)</td>
<td>0.9%</td>
<td>111</td>
<td>Carpenter 2010</td>
</tr>
</tbody>
</table>

**NOTE:** Some of these studies included a pre-emptive strategy for DNAemia.
RISK FACTORS FOR EBV-PTLD

High risk HSCT for development of EBV-related PTLD: allogeneic HSCT with any of the following risk factors:
- T-cell depletion (in vivo or ex vivo)
- EBV serology mismatch
- Cord blood transplantation
- HLA mismatch
- Acute / chronic GVHD requiring intensive immunosuppressive therapy
- High EBV viral load
- Splenectomy

The risk increases with the number of risk factors
PREVENTION OF EBV DISEASE
ALLOGENEIC STEM CELL TRANSPLANTATION (1)

- EBV DNAemia is common after HSCT and rarely causes significant problems through direct viral end-organ disease. The important complication of EBV infection is post-transplant lymphoproliferative disorder (PTLD).

- The prevention of PTLD is still of major importance in allogeneic HSCT patients at high risk, since the outcome of PTLD remains unsatisfactory.
ALLOGENEIC STEM CELL TRANSPLANTATION (2)

• All HSCT patients and donors should be tested for EBV antibodies, (All u).

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

• For EBV-seronegative patient, the risk of PTLD is higher when the donor is EBV-seropositive (BII u).

• For EBV-seropositive recipient, EBV-seropositive donor might be beneficial, due to presence of EBV+ CTL (CIII).
For allogeneic HSCT recipients at high risk for EBV-PTLD, prospective monitoring of EBV DNA-emia is recommended (All u).

Allo-HSCT recipients at high risk for EBV-PTLD should be closely monitored for symptoms or signs attributable to EBV infection and PTLD (All u).

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

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

- It is not recommended that conventional chemotherapy patients be routinely monitored for EBV (DIII).
DIAGNOSIS OF EBV DNA-EMIA
Prospective monitoring of EBV DNA by quantitative PCR is recommended after high-risk allo-HSCT (All u)

Material: the same preferences for whole blood, plasma, and serum (BII u)
SURVEILLANCE FOR EBV DNA-EMIA

• It is important to tailor to individual patients a monitoring strategy adapted to risk factors for development of EBV-PTLD

• Start to monitor: no later than 4 weeks after HSCT (according to risk factors) (AII u)

• Frequency:
  - screening (in EBV DNA negative pts) testing is recommended once a week (BII u)
  - in patients with rising EBV DNA more frequent sampling should be considered (BII u)

• End of screening: at least up to 4 months after HSCT in high risk patients; longer screening/monitoring is recommended in patients considered to have poor T-cell reconstitution or in those having experienced an early EBV reactivation (BII u).
DIAGNOSIS OF EBV DISEASE
DIAGNOSIS OF EBV-DISEASE / 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 (All u).

• Definitive diagnosis of EBV-PTLD requires biopsy and histological examination, including immunohistochemistry or flow cytometry.

• EBV detection requires detection of viral antigens or in situ hybridization for the EBER transcripts (All u).
DIAGNOSIS OF EBV-DISEASE / PTLD

• Non-invasive methods:
  - Quantitative EBV DNA-emia (blood, plasma, serum) (All u)
  - PET-CT or CT (BII t) in order to:
    - stage the disease
    - identify the most appropriate lesion for biopsy
    - document extranodal disease
      (PET-CT is superior to CT for extranodal disease)
    - assess response to therapy

• Invasive methods:
  - biopsy of lymph node and/or other sites suspected for EBV disease (All u)
PROPHYLAXIS OF EBV DISEASE
PROPHYLAXIS IN ALLO-HSCT RECIPIENTS

- B-cell depletion with prophylactic rituximab might reduce the risk of EBV DNAemia (CII u).
- High efficacy (no PTLD) of prophylactic EBV-CTLs in a high-risk group (CII u).
- There are no data to support any impact of antiviral drugs on the development of EBV-PTLD, so that antiviral drugs are not recommended (DII u).
- IVIG is not recommended for EBV prophylaxis (DIII).
PREEMPTIVE THERAPY
INDICATIONS FOR PREEMPTIVE THERAPY

It is not possible with current data to recommend fixed threshold values of EBV DNA-emia to initiate preemptive therapy.
<table>
<thead>
<tr>
<th>METHOD</th>
<th>PREEMPTIVE THERAPY</th>
<th>THERAPY OF PTLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>462/509 (90.8%)</td>
<td>205/316 (64.9%)</td>
</tr>
<tr>
<td>Rituximab + RI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTL (Cytotoxic T-lymphocytes)</td>
<td>101/101 (100%) prophylactic</td>
<td>53/70 (75.7%)</td>
</tr>
<tr>
<td></td>
<td>127/135 (94.1%) preemptive</td>
<td>(usually second-line therapy)</td>
</tr>
<tr>
<td>RI</td>
<td>38/44 (86.4%)</td>
<td></td>
</tr>
<tr>
<td>DLI</td>
<td></td>
<td>51/88 (57.9%)*</td>
</tr>
<tr>
<td>Rituximab + chemotherapy</td>
<td></td>
<td>23/56 (41.0%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(usually second-line therapy)</td>
</tr>
<tr>
<td>Rituximab + antivirals (CDV)</td>
<td>37/42 (92.5%)</td>
<td>38/60 (63.3%)</td>
</tr>
<tr>
<td>Antivirals (CDV)</td>
<td></td>
<td>21/62 (34.4%)*</td>
</tr>
</tbody>
</table>

RI – reduction of immunosuppression; DLI – donor lymphocyte infusion; CDV – cidofovir; (*) - in many cases other therapies were also used
PREEMPTIVE THERAPY FOR EBV DNA-emia

- Rituximab, 375 mg/m², once weekly (All u) max. 4 doses
  (NOTE: rituximab possibly reduces the risk of a/c GVHD)
- Reduction of immunosuppressive therapy, if possible (All u)
- Donor or third party EBV-specific cytotoxic T lymphocytes (CTL)
  (if available) (CII u)
- Antiviral drugs are not recommended for preemptive therapy (DII h)
TREATMENT OF PTLD
THERAPY IN PTLD: FIRST LINE

• Rituximab, 375 mg/m², once weekly (All u)
  (NOTE: rituximab possibly reduces the risk of a/c GVHD)

• Reduction of immunosuppressive therapy, if possible (All u)

• EBV-specific CTL, if available (CII u)
  - Donor or third-party EBV-specific CTL
THERAPY IN PTLD: SECOND LINE

- T-cell therapy: EBV-specific CTLs (CII u) or DLI in order to restore T-cell reactivity (BIII)

- Chemotherapy +/- rituximab is a potential option for PTLD therapy after failure of other methods (CII h)

- Antiviral agents are not recommended for PTLD therapy (DII h)

- IVIG is not recommended for PTLD (DIII)
THERAPY IN PTLD: CNS DISEASE

- Rituximab + chemotherapy (primary CNS lymphoma protocols) (BII h)
- Rituximab intravenous (CIII)
- Rituximab intrathecal (CIII)
- T-cell therapy (CIII)
- Radiotherapy (CIII)
THERAPY IN EBV-NEGATIVE and/or T-cell PTLD

• Since EBV-positive T-cell PTLD after HSCT has been extremely rare, T-PTLD should be regarded as malignant lymphoma and treated with respective chemotherapy (CIII).

• Very late (>5 years after HSCT) EBV-negative PTLD should also be regarded as malignant lymphoma and treated with respective chemotherapy (CIII).