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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Epstein-Barr virus-related post-transplant lymphoproliferative disorders are recognized as a significant cause of morbidity and mortality in patients undergoing hematopoietic stem cell transplantation. To better define current understanding of post-transplant lymphoproliferative disorders in stem cell transplant patients, and to improve its diagnosis and management, a working group of the Sixth European Conference on Infections in Leukemia 2015 reviewed the literature, graded the available quality of evidence, and developed evidence-based recommendations for diagnosis, prevention, prophylaxis and therapy of post-transplant lymphoproliferative disorders exclusively in the stem cell transplant setting. The key elements in diagnosis include non-invasive and invasive methods. The former are based on quantitative viral load measurement and imaging with positron emission tomography; the latter with tissue biopsy for histopathology and detection of Epstein-Barr virus. The diagnosis of post-transplant lymphoproliferative disorder can be established on a proven or probable level. Therapeutic strategies include prophylaxis, preemptive therapy and targeted therapy. Rituximab, reduction of immunosuppression and Epstein-Barr virus-specific cytotoxic T-cell therapy are recommended as first-line therapy, whilst unselected donor lymphocyte infusions or chemotherapy are options as second-line therapy; other methods including antiviral drugs are discouraged.
Introduction

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of diseases occurring in the setting of transplantation of either hematopoietic stem cells (HSCT) or solid organs (SOT). PTLD results from the uncontrolled neoplastic proliferation of lymphoid or plasma-cytic cells. It can occur at any age and after all types of transplant; recipients of allogeneic HSCT are at a particular risk for developing PTLD. In contrast to the SOT setting, post-HSCT PTLD are almost exclusively EBV-related, although rare cases of non-EBV-PTLD also exist in this setting. PTLD is one of the most severe complications associated with transplantation. Before 2000, an attributable mortality for PTLD of 84.6% after HSCT was reported. With the introduction of new approaches for EBV disease/PTLD, including the use of monitoring for EBV by PCR, pre-emptive therapy and timely treatment with rituximab, considerable improvements in outcome have been achieved. However, mortality remains high; approximately one-third of diagnosed patients.

Recently, guidelines for management of PTLD in the SOT setting were published. The first recommendations for management of EBV infections in patients undergoing HSCT or therapy for hematological malignancies were produced following the Second European Conference on Infections in Leukemia (ECIL-2) in 2007. The goal of this paper is to present updated recommendations based on analysis of recent data.

Methods

The main task of ECIL is to develop evidence-based guidelines for management of infectious complications in subjects with leukemia including HSCT. An EBV-PTLD Working Group was hence created. The group defined the relevant issues, questions and outcomes to be addressed, and evaluated these issues and questions prior to the consensus conference through a systematic literature review. PubMed was searched using each of the following terms: lymphoproliferative disorder, PTLD, Epstein-Barr virus, EBV, together with leukemia, hematopoietic transplantation, HSCT, bone marrow transplantation, or cord blood. Relevant studies were reviewed up to August 2015. Recommendations were elaborated within the group and graded for quality of evidence (I–III) and strength of recommendation (A–D) using the ESCMID/EFISG grading system (Table 1).

The ECIL-6 conference (September 11-12, 2015) was attended by 55 experts from 25 countries, including 16 European countries. Experts in hematology, microbiology, and infectious diseases were mostly selected for their active participation in the host organizations. The group presented its literature review and guideline proposals in plenary session. After panel debate, the recommendations were revised as necessary until reaching a final consensus.

Definitions and diagnostic criteria

Primary EBV infection is defined when EBV is detected (nucleic acid or serologically) in an EBV-naive individual (most often asymptomatic acquisition, or occasionally presenting as infectious mononucleosis). Recurrent EBV DNA-emia is diagnosed by detection of EBV DNA in the blood of a previously infected individual, as defined by detection of EBV-specific IgG-antibodies. EBV-associated disease following transplantation can be categorized as EBV-PTLD or other EBV-associated post-transplant manifestations; also referred to as EBV end-organ disease.

EBV-PTLD can be diagnosed as probable or proven. Probable EBV disease: significant lymphadenopathy, hepatosplenomegaly or other end-organ manifestations (without tissue biopsy, but in the absence of other documented cause), together with significant EBV DNA-emia. Proven EBV disease: detection of EBV nucleic acids or EBV-encoded proteins in a tissue specimen, together with symptoms and/or signs from the affected organ.

The diagnosis of EBV-PTLD should be based on at least two of the following histological features: (i) disruption of underlying cellular architecture by a lymphoproliferative process, (ii) presence of monoclonal or oligoclonal cell populations as revealed by cellular and/or viral markers, (iii) evidence of EBV infection in many of the cells i.e. DNA, RNA or protein. Detection of EBV nucleic acid in blood is not, eo ipso, sufficient for the diagnosis of EBV-PTLD.

The recommended method for histological specimens, conferring high sensitivity and specificity, is the detection of EBV-encoded RNA by in situ hybridization (EBER-ISH). Immunohistochemistry for viral proteins have good specificity but lower sensitivity; these proteins are variably expressed in PTLD biopsies. Detection of EBV DNA by PCR of histological extracts is not an appropriate method for PTLD diagnosis given the very high sensitivity but low positive predictive value (PPV) (Table 2).

The histopathologic criteria of PTLD were defined by Swerdlow and Greig. The WHO classification is most commonly used, with four types of morphological lesions being recognized: polyclonal early lesions, polymorphic, monomorphic (B-cell or T/NK-cell) and classical Hodgkin lymphoma-type PTLD.

Epidemiology

The incidence of EBV DNA-emia and EBV-PTLD varies between transplant centers. The reported incidence of EBV DNA-emia ranging between 0.1-65% is largely dependent on the type of transplant, assay sensitivity, defined level of DNA-emia, use of systematic screening and its timing.

In a recent EBMT study, the overall incidence of PTLD after allogeneic HSCT was 3.2%, varying from 1.2% in matched family donor (MFD) to 2.8% in mismatched family donor (haploidentical/MMFD), 4.0% in matched unrelated donor (MUD), and 11.2% in mismatched unrelated donor (MMUD) recipients. In recipients of unrelated cord blood (CBT), the incidence of EBV-PTLD was 2.6-3.3% for myeloablative transplants, and 7-12.9% in non-myeloablative transplants. Interestingly, data from haplo-HSCT incorporating post-transplant cyclophamide (haplo-PTCy-HSCT) indicate a very low EBV-PTLD incidence. The median time to development of PTLD after HSCT is 2-4 months. Only 4% of cases develop later than 12 months after HSCT, and cases occurring >5 years after HSCT are extremely rare. PTLD after autologous-HSCT is very rare.

Risk factors for EBV-PTLD

Risk factors for developing EBV-PTLD can be considered as existing pre- or developing post-transplant (Table 3). Importantly, assessing the risk of EBV-PTLD is
dependent on the HSCT context with potentially complex interactions between the primary hematological malignancy, HSCT procedure, source, and other factors. Given that the risk of EBV-PTLD is predominantly related to the degree of T-cell depletion or impairment, this should be regarded as the principal risk factor (Allu). Strategies that deplete T cells from the graft increase the risk of EBV-PTLD.38

CBT confers an intrinsic risk for EBV-PTLD because of T-cell naïvety related to the HSC source. A high incidence of EBV-PTLD in both pediatric and adult patients after CBT, following reduced intensity conditioning regimens using anti-thymocyte globulin (ATG) or alemtuzumab (anti-CD52), has also been reported.28 This likely reflects both the delayed recovery of EBV-specific CTLs after such transplants, alongside the persistence of recipient-derived B cells. The use of alemtuzumab during conditioning in other types of HSCT can also be regarded as a risk factor for EBV-PTLD.27,29 There appears to be a dose-dependent risk with the in vivo use of ATG in children,40 which is probable also in adults. Current data do not suggest any significant differences between children and adults with respect to epidemiology and risk factors.

Patients undergoing HSCT can be classified for the risk for EBV-PTLD as low risk (auto-HSCT), standard risk (MFD allo-HSCT without risk factors, haplo-PTCy-HSCT), and high risk (MFD with at least one risk factor, MUD/MMUd, alternative donors including CBT).

**ECIL recommendations for prevention of EBV diseases including PTLD**

ECIL recommends that all allo-HSCT patients and donors should be tested for EBV antibodies before transplantation (Table 4). Since EBV sero-mismatch is a risk factor for PTLD,24,25 the selection of an EBV matched donor, if possible, might be beneficial. As EBV-PTLD after HSCT is usually of donor origin and EBV might be transmitted with the graft, the risk of EBV-PTLD is higher when the donor is seropositive. Neither in vivo/ex vivo CD34-positive selection nor CD3/CD19 depletion prevents EBV-PTLD.21,35 Allo-HSCT recipients should be closely monitored clinically, together with prospective monitoring for EBV DNA in peripheral blood. Importantly, monitoring and intervention strategies might be individualized, informed by a holistic assessment of EBV-PTLD risk.

**ECIL recommendations for diagnosis and monitoring of EBV DNA-emia**

Prospective monitoring of EBV DNA performed by quantitative PCR is recommended. There are no data to support a preference for whole blood, plasma or serum; all are appropriate specimens for monitoring EBV DNA-emia.7,41-43 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%.3 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 56 hours,7 more frequent sampling in patients with rising EBV DNA-emia may be warranted (Table 5).
Table 2. Relative merits of EBV assays.

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<tr>
<th>Assay</th>
<th>Material</th>
<th>Value</th>
<th>Recommendation</th>
<th>Reference</th>
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<tbody>
<tr>
<td>DNA by PCR</td>
<td>Whole blood, plasma, serum</td>
<td>high sensitivity and specificity, low PPV</td>
<td>Allu</td>
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<tr>
<td></td>
<td>Tissue specimen</td>
<td>very high sensitivity but low PPV</td>
<td>Dilu</td>
<td></td>
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<tr>
<td>EBER ISH</td>
<td>Tissue specimen</td>
<td>high sensitivity and specificity</td>
<td>Allu</td>
<td></td>
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<tr>
<td>Viral proteins</td>
<td>Tissue specimen</td>
<td>high sensitivity but lower</td>
<td>CIII</td>
<td></td>
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<tr>
<td>(e.g. LMP 1 and EBNA1)</td>
<td></td>
<td>sensitivity, variably expressed</td>
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<td>in PTLD biopsies</td>
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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

frequently associated with rapidly progressive multi-organ failure and death. The diagnostic approach to EBV-PTLD should, preferably, be based on biopsies of enlarged lymph nodes and other sites of suspected EBV disease (Table 3). However, if this is impossible due to the clinical status of the patient, a non-invasive approach, encompassing quantitative EBV DNAemia combined with PET-CT/CT imaging, can be considered.

The diagnostic work-up of EBV-PTLD includes: (a) physical examination, including an examination for fever, tonsillitis, adenopathy and organomegaly; (b) PET-CT/CT imaging; (c) endoscopy in case of gastro-intestinal symptoms; (d) tissue biopsy with histological examination, including EBER ISH and/or immunohistochemistry for viral antigens, and/or flow cytometry; (e) peripheral blood EBV viral load by PCR.

The clinical staging of EBV-PTLD includes: nodal vs. extranodal, limited (unifocal) vs. advanced (multifocal) disease. The Ann Arbor classification, established for staging of lymphoma, can also be recommended. As PTLD is an FDG-avid malignancy, EBV-PTLD can be staged according to the Lugano classification by PET-CT, both in children and adults.

Management strategies
There are three approaches for EBV infection, EBV disease and EBV-PTLD after HSCT: prophylaxis, pre-emptive therapy and treatment of EBV disease/PTLD. Prophylaxis of EBV disease includes any intervention (e.g. drug or cellular therapy) given to an asymptomatic EBV-seropositive patient to prevent EBV DNAemia. Pre-emptive therapy includes any intervention given to a patient with EBV DNAemia to prevent EBV disease. Treatment of EBV disease includes therapeutic interventions for patients with probable or proven EBV disease.

Prophylaxis and treatment approaches of EBV-PTLD include: administration of rituximab (anti-CD20 monoclonal antibodies), reduction of immunosuppression (RI), EBV-CTL, donor lymphocyte infusion (DLI) and chemotherapy. RI is defined as a sustained decrease of at least 20% of the daily dose of immunosuppressive drugs with the exception of low-dose corticosteroid therapy.

Pooling results from published studies in HSCT recipients suggest that administration of rituximab results in a positive outcome for approximately 90% patients treated pre-emptively, and 65% with EBV-PTLD. Recent data demonstrate that RI, when applied in combination with rituximab, appears to improve the outcome by over 80%. The use of EBV-CTLs leads to a positive outcome for >90% of patients treated pre-emptively, and approximately 75% in therapy of EBV-PTLD. There are no studies directly comparing efficacy of rituximab±RI vs. EBV-CTL in either prophylaxis, pre-emptive or targeted therapy. Thus, there is insufficient evidence to support a recommendation for one treatment modality over another as a first line approach for centers with access to both therapies.

ECIL recommendations for prophylaxis of EBV DNAemia

Rituximab. B-cell depletion by prophylactic use of rituximab before or shortly after allo-HSCT might reduce the risk of EBV DNAemia and PTLD (Table 4). In a large retrospective analysis, prophylactic post-transplant rituximab significantly reduced the risk of EBV DNAemia; however, no statistically significant impact on PTLD incidence, treatment-related mortality, and overall survival in comparison to a pre-emptive approach was demonstrable. Low risk of EBV-PTLD was observed also after the use of post-transplant high-dose cyclophosphamide, or sirolimus as GvHD prophylaxis. Since rituximab treatment after allo-HSCT has been related to an increased risk of life-threatening cytopenias and bacterial infections,
the use of rituximab should be restricted to patients at highest risk of EBV-PTLD and, following its use, accompanied by close monitoring for hypogammaglobulinemia with consideration of Ig replacement and other strategies to limit infectious-related mortality.

**EBV-CTLs.** High efficacy of prophylaxis has been shown with the use of EBV-CTLs in a high-risk group in one study. Current use of EBV-CTLs is, however, limited as it is available only in selected centers.

**Antiviral drugs.** Although aciclovir, ganciclovir, foscarnet, and cidofovir show some in vitro activity against replicating EBV, antiviral treatment of latent EBV has been unsuccessful since latently infected B cells do not express the EBV thymidine kinase enzyme transcript or protein. There is no evidence to recommend any anti-EBV antiviral prophylaxis in patients with hematological malignancies in non-allo-HSCT setting (DIII).

**ECIL recommendations for preemptive therapy against EBV disease**

**Indications.** The indication for preemptive therapy is significant EBV DNA-emia without clinical symptoms/disease in patients with high risk for EBV-PTLD (Table 7). The goal of preemptive therapy is to obtain a negative EBV PCR or EBV DNA-emia below the initial threshold without relapse.

**Implications of EBV DNA-emia.** EBV DNA-emia mostly occurs prior to the onset of clinical symptoms but data are somewhat conflicting. Currently available data do not allow elucidation of an EBV-DNA threshold for the development of EBV disease. Indeed, probable/proven PTLD has been described in a significant proportion of patients with EBV DNA levels below commonly adopted intervention thresholds.

**Threshold value.** In the absence of universal standards for Nucleic Acid Test assays, ECIL cannot recommend a specific threshold value of EBV DNA-emia for giving preemptive therapy. Some authors employ a threshold of 1,000 EBV copies/mL, 10,000 EBV copies/mL, or 40,000 EBV copies/mL when determined in whole blood, plasma, serum; or 1,000 copies as determined per 10^5 PBMC to initiate pre-emptive therapy. The rate of increase of EBV copy number is likely to be clinically significant given that increases in EBV DNA-emia are due to the expansion of EBV-infected memory B cells in the peripheral blood. Local experience based on correlation of clinical and laboratory data might be a rationale for center-specific cut-off value.

**Rituximab.** The primary method for preemptive therapy is rituximab, dose 375 mg/m^2, once weekly until EBV DNA-emia negativity. The number of doses should be assessed locally on the basis of changes in EBV DNA-emia and an assessment of the patient’s immune function. Typically, 1-4 doses are sufficient.

**Reduction of immunosuppression.** Rituximab should be
combined with RI, if possible, except in patients with uncontrolled severe acute or chronic GvHD.

Other options. Donor or third party EBV-specific cytotoxic T lymphocytes (CTL) are highly efficacious; however, this approach is not widely available. Antiviral drugs are not effective against EBV.

ECIL recommendations for treatment of EBV-PTLD

First line therapy. In case of proven or probable EBV-PTLD, therapy should be started as soon as practicable due to the risk of a rapidly growing high-grade lymphoid tumor, together with the risk of multi-organ impairment. Rituximab monotherapy is the treatment of choice for EBV-PTLD (Table 8) with positive outcome reported in almost 70% of patients. Rituximab is usually administered once weekly for up to 4 doses while monitoring EBV viral load. Additional doses might result in down-regulation of CD20 expression and thereby possibly decreased efficacy. Reduction of immunosuppression (RI) is rarely successful once weekly for up to 4 doses while monitoring EBV viral load. Additional doses might result in down-regulation of EBV-P TCL (Table 8) with positive outcome reported in CNS. To date, no standard therapy has been accepted. Possible therapeutic options include: (i) chemotherapy±rituximab in line with primary CNS lymphoma protocols based on high dose methotrexate and/or cytarabine or hydroxyurea; (ii) monotherapy with rituximab, either systemic or intrathecal; (iii) T-cell therapy with EBV-specific CTLs; (iv) radiotherapy.

Response to therapy. The treatment goal is resolution of all signs and symptoms of PTLD, including a negative viral load. Response to rituximab therapy can be identified by a decrease in EBV DNA-emia of at least 1 log in the first week of treatment (BII).

Second line therapy. In the setting of rituximab failure, second-line therapy options include cellular therapy (DLI or CTLs) or chemotherapy±rituximab. Unselected DLI from an EBV-positive donor are employed to restore broad T-cell reactivity, including EBV-specific responses; unselected DLI, however, can be associated with severe GvHD. Previous GvHD is usually a contraindication to DLI. ECIL’s preferred approach is specific cellular therapy; however, EBV-specific CTLs are not readily available in all centers. Apart from donor-derived CTLs, the

Table 6. Recommendations for prophylaxis against EBV disease.

<table>
<thead>
<tr>
<th>Recommendations for prophylaxis against EBV disease</th>
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<tr>
<td>* B-cell depletion with prophylactic rituximab might reduce the risk of EBV DNA-emia (CIIu).</td>
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<tr>
<td>* Prophylactic use of EBV-CTLs should be considered as first line prophylactic treatment whenever possible (CIIu).</td>
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<tr>
<td>* There are no data to support any positive impact of antiviral drugs on the development of EBV-PTLD. Antiviral drugs are not recommended for EBV prophylaxis (DIIu).</td>
</tr>
<tr>
<td>* Interferon and IVIG are not recommended for EBV prophylaxis (DIIu).</td>
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Table 7. Recommendations for preemptive therapy of EBV disease.

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<thead>
<tr>
<th>Recommendations for preemptive therapy of EBV disease</th>
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<tr>
<td>* Significant EBV DNA-emia without clinical symptoms of EBV disease is an indication for preemptive therapy with rituximab (BIIu).</td>
</tr>
<tr>
<td>* No specific threshold of EBV DNA-emia can currently be recommended for initiation of preemptive therapy.</td>
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<tr>
<td>* Rituximab once weekly (1-4 doses) is recommended until EBV DNA-emia negativity (Alu).</td>
</tr>
<tr>
<td>* Rituximab should be combined with reduction of immunosuppression, if possible (Alu).</td>
</tr>
<tr>
<td>* Donor or third party EBV-specific cytotoxic T lymphocytes (CTL) should be considered, if available (CIIu).</td>
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<tr>
<td>* Antiviral drugs are not recommended for preemptive therapy (DIIu).</td>
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Table 8. Recommendations for therapy of EBV-PTLD.

<table>
<thead>
<tr>
<th>First line therapy in EBV-PTLD</th>
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<tr>
<td>1. Rituximab, 375 mg/m², once weekly (Alu).</td>
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<tr>
<td>2. Reduction of immunosuppressive therapy combined with rituximab should always be considered, if possible (Alu).</td>
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<tr>
<td>3. Cellular therapy as adoptive immunotherapy with in vitro generated donor or third-party EBV-specific CTL, if available (CIIu).</td>
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<th>Second line therapy in EBV-PTLD</th>
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<tr>
<td>1. Cellular therapy (EBV-specific-CTLs or DLI) (BIII).</td>
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<tr>
<td>2. Chemotherapy±rituximab is a potential option after failure of other methods (CIIb).</td>
</tr>
<tr>
<td>3. Surgery, IVIG, interferon and antiviral agents are not recommended for therapy of PTLD (DIII) CNS EBV disease.</td>
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<th>CNS EBV disease</th>
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<td>* Therapeutic options in EBV-PTLD in central nervous system include: rituximab±chemotherapy (BIIb), rituximab systemic or intrathecal monotherapy (CIII), anti-EBV T-cell therapy (CIII) or radiotherapy (CIII).</td>
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novel development of 3rd-party EBV-CTLs may represent a promising option for the recipients of cord blood transplant, or those who have EBV-negative donors and/or donors who are unable to provide further donation for cellular therapy. Data on efficacy of DLI or chemotherapy in EBV-PTLD are limited. Chemotherapy for EBV-PTLD after HSCT is not recommended as first-line therapy due to poor tolerability in HSCT patients and the risk of inducing neutropenia and graft failure. Chemotherapy for EBV-PTLD is therefore restricted for refractory/relapsing cases.

**Possible future developments**

The possible future anti-EBV prophylaxis and/or therapies include cellular therapy, new monoclonal antibodies and new antivirals. Active immunisation against EBV is not available. Ex vivo-generated EBV-CTL have proved to be an effective prophylactic measure, pre-emptive therapy, or treatment for PTLD post-HSCT. EBV-CTL can be isolated and expanded ex vivo from EBV-seropositive stem cell or third-party donors. Considering the recent success and safety profile of obinutuzumab in CD20-positive malignant lymphomas, novel anti-CD20 monoclonal antibodies are possible candidates for future use in EBV-PTLD. The possibility of new and experimental therapies for EBV-PTLD has also recently emerged in the transplant setting, including brentuximab vedotin, anti-CD30 antibodies. Brincidofovir, a new, currently unlicensed antiviral agent, has excellent antiviral activity against EBV in vitro. Further study, however, is needed in order to establish whether prophylaxis with this drug will be able to reduce the risk of EBV replication and possibly EBV-PTLD.

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