Successful treatment of lymphoproliferative disease complicating primary immunodeficiency/immunodysregulatory disorders with reduced-intensity allogeneic stem-cell transplantation

Jonathan M. Cohen,1,2 Neil J. Sebire,3 Julia Harvey,1 H. Bobby Gaspar,1,5 Cale Cathy,1 Alison Jones,1 Kanchan Rao,4 David Cubitt,6 Persis J. Amrolia,4,5 E. Graham Davies,1,5 and Paul Veys4

1Department of Clinical Immunology, Great Ormond Street Hospital, London; 2Infectious Diseases and Microbiology Unit, Institute of Child Health, University College London, Departments of 3Histopathology and 4Bone Marrow Transplantation, Great Ormond Street Hospital, London; 5Molecular Immunology Unit, Institute of Child Health, University College London; 6Department of Virology, Great Ormond Street and Hospital, London, United Kingdom

Lymphoproliferative disease (LPD) is a recognized complication of primary immunodeficiency (PID) and immunodysregulatory syndromes. Historically, it has a very poor outcome. For patients surviving LPD, myeloablative hematopoietic stem cell transplantation (SCT) was the only cure for the underlying PID, with a high risk of developing posttransplantation complications, including recurrent lymphoproliferative disease. We describe 8 patients with a range of PID and immunodysregulatory syndromes complicated by LPD. After initial treatment of the LPD (including the use of anti-CD20 monoclonal antibody, rituximab, in 6 of the patients), all patients underwent reduced-intensity conditioning (RIC) SCT with prospective monitoring for Epstein-Barr virus (EBV) viremia. After transplantation, 3 patients received rituximab, and 3 patients received prophylactic EBV-specific cytotoxic T-lymphocytes. Only 1 patient developed recurrent LPD posttransplantation, which responded to rituximab. All patients who underwent transplantation survive free of LPD and are cured of their PID at a median follow-up of 4 years (range, 1-7 years). With careful monitoring and pre-emptive therapy, we advocate this RIC SCT approach to patients with PID who have pre-existing EBV-LPD. (Blood. 2007;110:2209-2214)

Introduction

Lymphoproliferative disease (LPD) can arise in a range of situations where there is impaired immunity, and is a recognized complication of primary immunodeficiency (PID) and immunodysregulatory syndromes. In PID-associated LPD (PID-LPD), the disease is most commonly extranodal, B-cell in origin and driven by Epstein-Barr virus (EBV).1 Typical predisposing PIDs include Wiskott-Aldrich syndrome, ataxia telangiectasia, X-linked lymphoproliferative syndrome (XLP), common variable immunodeficiency, and hyper-IgM syndrome.2,4

Historically, the outcome of PID-LPD was very poor, with reported mortality rates nearing 70% when the disease was unresponsive to conventional chemotherapy.2 Such aggressive disease was associated with poor T-cell function, and not to any particular histopathologic characteristic aspect of the LPD. When patients with PID survived LPD, myeloablative hematopoietic stem cell transplantation (SCT) offered the only opportunity for cure of the underlying PID. Morbidity from both the underlying complications of PID, including LPD and its therapy, led to high transplantation-related mortality for such patients. Furthermore, the very high risk of developing posttransplantation lymphoproliferative disease (PTLD) would often preclude SCT.

Several recent advances have made transplantation for PID possible in patients with LPD. Organ-toxic chemotherapeutic regimens have been superseded in many cases by the use of rituximab to treat the LPD, and patients with PID can now be offered less-toxic (although heavily immunosuppressive) reduced-intensity conditioning (RIC) SCT regimes to cure the underlying PID.3 Although recent reports have suggested that RIC SCT in this group may be associated with an increased risk of PTLD.9 Similar RIC regimes have been used to treat adults with LPD arising de novo,7 suggesting that myeloablative regimes may not be necessary to control these diseases. After SCT, the combination of molecular screening for EBV viremia and prophylactic/pre-emptive therapy with rituximab8 and EBV-specific cytotoxic T lymphocytes (CTLs) significantly reduces the risk of the development of PTLD.9

Here we describe our experience using this approach to achieve a long-term cure of LPD in patients with PID.

Patients, materials, and methods

During the period between 1999 and 2006, 8 children presented with LPD-complicating PID or immunodysregulatory syndromes at Great Ormond Street Hospital. Their details are displayed in Table 1. A total of 5 patients had primary immunodeficiencies; the other 3 had evidence of an immunodysregulatory disorder. Although the LPD was clinically heterogeneous, histologically most patients had either monomorphic LPD with a phenotype of diffuse large B-cell lymphoma, or Hodgkin disease. Biopsies from 5 patients showed evidence of EBV by in situ hybridization for EBV-encoded RNA (EBER). Biopsies in 2 patients showed no evidence that the LPD was driven by EBV.

LPD in 5 of 6 patients responded to chemotherapy; the other patient (no. 3) required rituximab to control disease. A total of 2 patients relapsed following chemotherapy; 1 patient (no. 5) relapsed twice. Patients 1 and 5...
Table 1. Details of patients with primary immunodeficiency/immunodysregulatory syndromes complicated by LPD undergoing hematopoetic SCT

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Immunologic abnormality</th>
<th>Age at LPD, y</th>
<th>LPD clinical</th>
<th>LPD histology</th>
<th>EBV-ISH (EBER)</th>
<th>LPD therapy</th>
<th>EBV load at start of transplantation</th>
<th>Therapy at time of BMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>Undefined CID</td>
<td>Low IgA, low IgM, poor PHA response</td>
<td>12</td>
<td>Retroperitoneal and pulmonary disease</td>
<td>Monomorphic LPD—DLBCL</td>
<td>+</td>
<td>COP (no response), followed by rituximab</td>
<td>Detected (not quantified)</td>
<td>Weekly rituximab</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>WAS</td>
<td>Poor PHA</td>
<td>17</td>
<td>Cutaneous lesion right thigh*</td>
<td>Monomorphic LPD—LyG</td>
<td>+</td>
<td>Rituximab 4 times</td>
<td>Not detected</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>IE</td>
<td>No specific laboratory abnormality identified</td>
<td>2</td>
<td>Cervical lymphadenopathy and pulmonary infiltration</td>
<td>Monomorphic LPD—DLBCL</td>
<td>+</td>
<td>COP 4 times, followed by rituximab</td>
<td>Not detected</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>Undefined CID</td>
<td>Low IgM, poor PHA</td>
<td>2</td>
<td>Cervical lymphadenopathy</td>
<td>HD—mixed cellularity</td>
<td>+</td>
<td>CHVPP 6 times; local recurrence after 2 mo, Rx mini-BEAM and local DXT</td>
<td>Not detected</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>ALPS-like</td>
<td>6% DN T cells; absent B cells, low CD4 cells</td>
<td>6</td>
<td>Cervical lymphadenopathy</td>
<td>HD stage 1A</td>
<td>Unknown</td>
<td>Chemotherapy and local DXT; 1st relapse: Rx ABDV 6 times; 2nd relapse (stage IV disease): Rx ifosfamide/cisplatinum/etoposide</td>
<td>Not detected</td>
<td>Weekly rituximab</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>CHH</td>
<td>Absent PHA, lymphopenia</td>
<td>11</td>
<td>Liver lesion, pleural effusion, CNS involvement on MRI brain</td>
<td>Monomorphic LPD—DLBCL</td>
<td>+</td>
<td>COP, followed by rituximab; IT MTX/steroids</td>
<td>Not detected</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>XLP</td>
<td>Absent SAP expression</td>
<td>3</td>
<td>Small bowel tumor complicated by perforation</td>
<td>Monomorphic LPD—DLBCL</td>
<td>–</td>
<td>COP, surgical resection, COPADM 2 times</td>
<td>Not detected</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>ALPS-like (DALD)</td>
<td>Not tested (on immunosuppressive therapy)</td>
<td>7</td>
<td>Abdominal and thoracic lymphadenopathy with lung infiltrates</td>
<td>Large T-cell small B-cell angioimmunoblastic LPD</td>
<td>–</td>
<td>Rituximab and steroids</td>
<td>Not detected</td>
<td>None</td>
</tr>
</tbody>
</table>

EBV-ISH indicates EBV in situ hybridization; CID, combined immunodeficiency manifesting as lymphopenia, poor mitogen responses, hypogammaglobulinemia, and recurrent infections; WAS, mutation-confirmed Wiskott-Aldrich syndrome; ALPS-like, autoimmune lymphoproliferative syndrome without confirmation of genetic mutation; CHH, cartilage-hair hypoplasia; IE, intractable ulcerating enterocolitis of infancy; XLP, x-linked lymphoproliferative syndrome; LyG, lymphomatoid granulomatosis; DLBCL, diffuse large B-cell lymphoma; HD, Hodgkin disease; COP, cyclophosphamide/vincristine/prednisolone; CHIVPP, chlorambucil/vincristine/prednisolone/procarbazine; BEAM, carmustine/etoposide/cytarabine/melphalan; DXT, radiotherapy; ABVD, adriamycin/bleomycin/vincristine/dacarbazine; MTX, methotrexate; COPADM, cyclophosphamide/vincristine/prednisolone/adriamycin/methotrexate; and DN, double-negative.

* Previously reported.10
were maintained on weekly rituximab until transplantation. In total, 6 patients received rituximab prior to transplantation to treat their LPD. All 8 patients received nonmyeloablative RIC SCT. Due to significant pre-existing organ dysfunction, Patient 1 was conditioned with low-dose total-body irradiation (TBI). She received peripheral blood stem cells from a matched sibling donor, with both cyclosporin A (CSA) and mycophenolate mofetil (MMF) as graft-versus-host disease (GVHD) prophylaxis. All other patients received 150 mg/m² fludarabine (in 5 divided doses), 140 mg/m² melphalan, and 1 mg/kg alemtuzumab (in 5 divided doses), with CSA as GVHD prophylaxis. The 2 patients who were single C-antigen HLA-mismatched also received MMF. No grafts were T-depleted ex vivo. Infection prophylaxis included aciclovir, oral ciprofloxacin, cotrimoxazole, intravenous immunoglobulin, itraconazole, and phenoxymethylpenicillin as described previously. The 2 patients with previous cryptosporidial disease also received azithromycin and paromomicin. As bone marrow transplantation (BMT) was undertaken to cure both the underlying immunologic condition as well as the secondary LPD, a cure was defined to include resolution of both problems as judged by clinical and immunologic parameters. Patients were monitored after transplantation with regular assessment of immune function and chimerism, as described previously.

Patients 1 through 4, treated prior to October 2003, were screened for EBV viremia weekly by DNA polymerase chain reaction (PCR) amplification of the EBV internal repeat region on whole blood. If EBV DNA was detected in whole blood, a semiquantitative assay to determine viral load was performed using serial dilutions of patient plasma. For patients 5 through 8, screening was performed with real-time quantitative PCR using whole blood. Patients were closely monitored for symptoms attributable to EBV and PTLD. Those with EBV viremia were categorized as either (1) asymptomatic, (2) symptomatic viremia (fever for which no other cause could be identified), or (3) PTLD.

Rituximab was used at doses of 375 mg/m² on a weekly basis in patients with rising EBV viremia, even in the absence of symptoms. Polyclonal EBV-specific CTLs were generated ex vivo under Good Manufacturing Practice conditions at the Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas, by repetitive stimulation of donor T cells from seropositive donors with EBV-transformed autologous lymphoblastoid cell lines.

Results

The incidence, manifestations, and treatment of post-SCT EBV viremia in the 8 patients who underwent transplantation are shown in Table 2. Patient 1 went into transplantation with EBV viremia associated with a fever, which settled with 5 once-weekly doses of rituximab.

The symptoms and viral load settled following 3 doses of rituximab and a reduction in immunosuppression. The highest viral load among patients not receiving rituximab or EBV CTLs was 50 000 copies/mL.

A total of 3 patients also developed cytomegalovirus (CMV) viremia, 1 with retinitis requiring a ganciclovir implant. A further patient had retinitis due to varicella zoster virus (VZV).

Of the 2 patients who had a reduction in immunosuppression to treat EBV, 1 (Patient 4) developed skin GVHD as a result, responding to topical steroids. Details of other complications are shown in Table 2.

These patients have been followed up for a median of 4 years (range, 1-7 years) (see Table 3). All patients have survived, and are currently clinically well. A total of 7 patients had full donor chimerism at initial engraftment in both lineages. In Patient 3, this dropped to high-level mixed chimerism by 1 year after transplantation, but has remained stable at that level since. Patient 1 achieved high-level mixed chimerism at initial engraftment, and this has remained stable since.

A total of 5 patients have normal immunologic competence, and 6 patients no longer require replacement immunoglobulin. Patient 2 has poor antibody responses and, after an episode of pneumococcal sepsis, was recommenced on replacement immunoglobulin. Although clinically well, Patient 1 still has poor vaccine responses and remains on replacement immunoglobulin 7 years after transplantation. Patient 8 has a normal PHA response, but low B and CD4 T cells at just under 1 year following transplantation. For Patient 3, who suffered from intractable enterocolitis of infancy (IE), good immune reconstitution has resulted in resolution of his diarrhea and reversal of his ileostomy.

Discussion

LPD can arise in a broad range of congenital disorders of the immune system, contributed to by both defective cellular immunity and disordered immune homeostasis. Disorders of immune homeostasis giving rise to LPD include XLP, autoimmune lymphoproliferative syndrome (ALPS), and Dianzani autoimmune lymphoproliferative disease (DALD). IE is a rare immune dysregulatory syndrome presenting in the neonatal period with panenteritis due to an unknown immunologic disorder, with a significant risk of developing LPD. In this series of pretransplantation PID-LPD, 5 patients had evidence of EBV infection driving the process against a background of abnormal immunity. In the 2 patients without evidence of EBV, LPD is likely to be attributable solely to impaired immune control.

LPD associated with primary immunodeficiencies represents a heterogeneous pathologic category; in most cases, the increased risk is thought to be due directly to defective immune surveillance. Therefore, the phenotype of the diseases occurring in this setting may be highly variable, although diffuse large B-cell lymphoma (similar to monomorphic subtype of PTLD) is the most common subtype, with Hodgkin disease–like LPD and other phenotypes more rarely described, as demonstrated in the current series. Hodgkin disease–like LPD may be more problematic for diagnosis with the distinction between classical Hodgkin lymphoma and Hodgkin-like LPD being blurred, because in many cases EBV expression can be detected by in situ hybridization, as was the case with at least 1 of the patients with Hodgkin disease studied here.
<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Age at BMT, y</th>
<th>Type of BMT</th>
<th>Conditioning</th>
<th>Initial donor chimerism (mononuclear cells)</th>
<th>Initial donor chimerism (Granulocytes)</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
<th>Time to EBV viremia</th>
<th>Max EBV load</th>
<th>Treatment for EBV</th>
<th>EBV clinical category</th>
<th>PTLD</th>
<th>PTLD therapy</th>
<th>PTLD outcome</th>
<th>Other complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Undefined</td>
<td>13 MSD PBSCT</td>
<td>TBI 200 cGy single fraction</td>
<td>CS/AMMF</td>
<td>Mixed (high level)</td>
<td>Mixed (high level)</td>
<td>No</td>
<td>No</td>
<td>Pre-BMT</td>
<td>17 900†</td>
<td>Rituximab continued from before transplantation</td>
<td>Fever but no PTLD</td>
<td>NA</td>
<td>NA</td>
<td>CMV retinitis (GCV implant); gastrointestinal obstruction due to adhesions</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>WAS</td>
<td>18 MUD BMT</td>
<td>Camp/Flu/ Melph</td>
<td>CSA</td>
<td>Full</td>
<td>Full</td>
<td>No</td>
<td>No</td>
<td>D59</td>
<td>100 000†</td>
<td>Rituximab 2 times (D74, D81); EBV CTLs (D130)</td>
<td>Asymptomatic</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>Cryptosporidial diarrhea; Pleural effusions</td>
</tr>
<tr>
<td>3</td>
<td>IE</td>
<td>6 MUD BMT</td>
<td>Camp/Flu/ Melph</td>
<td>CSA</td>
<td>Full</td>
<td>Full</td>
<td>Grade 3 skin/gut</td>
<td>No</td>
<td>D56</td>
<td>10 000†</td>
<td>EBV-CTLs (D160)</td>
<td>Asymptomatic</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Undefined</td>
<td>4 MFD BMT</td>
<td>Camp/Flu/ Melph</td>
<td>CSA</td>
<td>Full</td>
<td>Full</td>
<td>Grade 1 skin</td>
<td>No</td>
<td>D31</td>
<td>10 000†</td>
<td>No</td>
<td>PTLD</td>
<td>Liver lesions, cervical lymph nodes, fever, rash</td>
<td>Rituximab 3 times Full resolution</td>
<td>VZV retinitis</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>ALPS</td>
<td>8 MUD PBSCT</td>
<td>Camp/Flu/ Melph</td>
<td>CSA</td>
<td>Full</td>
<td>Full</td>
<td>No</td>
<td>Mild limited skin</td>
<td>D117</td>
<td>5 000†</td>
<td>No</td>
<td>Asymptomatic</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>CMV viremia</td>
</tr>
<tr>
<td>6</td>
<td>CHH</td>
<td>11 MUD BMT</td>
<td>Camp/Flu/ Melph</td>
<td>CSA</td>
<td>Full</td>
<td>Full</td>
<td>Grade 1 skin</td>
<td>Mild limited skin</td>
<td>D22</td>
<td>27 000†</td>
<td>Rituximab</td>
<td>Fever but no PTLD</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>Pulmonary aspergillosis</td>
</tr>
<tr>
<td>7</td>
<td>XLP</td>
<td>12 1C-MMUD PBSCT</td>
<td>Camp/Flu/ Melph</td>
<td>CS/AMMF</td>
<td>Full</td>
<td>Full</td>
<td>No</td>
<td>No</td>
<td>D141</td>
<td>50 000†</td>
<td>EBV-CTLs (D120)</td>
<td>Asymptomatic</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>Adenoviremia; seizures; pulmonary fungal infection</td>
</tr>
<tr>
<td>8</td>
<td>DALD</td>
<td>7 1C-MMUD BMT</td>
<td>Camp/Flu/ Melph</td>
<td>CS/AMMF</td>
<td>Full</td>
<td>Full</td>
<td>Grade 1 skin</td>
<td>Never detected</td>
<td>NA</td>
<td>NA</td>
<td>Asymptomatic</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>CMV viremia</td>
<td></td>
</tr>
</tbody>
</table>

MSD indicates matched sibling donor; MUD, matched unrelated donor; MFD, matched family donor; 1C-MMUD, 1C-antigen–mismatched unrelated donor; PBSCT, peripheral blood SCT; Camp, alemtuzumab 1 mg/kg; Flu, fludarabine 150 mg/m²; Melph, melphalan 140 mg/m²; GCV, ganciclovir; and NA, not applicable.

*Maximum EBV load measured by semiquantitative PCR (see “Patients, materials, and methods”).
†Maximum EBV load measured by quantitative PCR (see “Patients, materials, and methods”).
Initial studies suggested that polymorphic PTLD could be monoclonal or polyclonal, whereas most monomorphic PTLDs are monoclonal. However, molecular analysis reveals that virtually all cases of both polymorphic and monomorphic PTLDs are monoclonal. Thus, the assessment of clonality by molecular techniques does not add significantly clinically important prognostic information.

Most LPDs in the setting of primary immunodeficiency/immunodysregulation are aggressive, and the prognosis appears to be related to both the specific underlying immune disorder and the specific subtype of lymphoproliferation. Such cases are generally reported histopathologically according to their phenotype, and although precursor lesions have been reported in primary immunodeficiencies, the distinct categories of early lesions and polymorphic and monomorphic PTLD used in the posttransplantation setting may not be directly applicable in this setting, although they are commonly used.

The largest previous report of the outcome of LPD in the PID setting described 12 patients with similar predominance of large B-cell lymphoma. Of these 12 patients, 9 died, 4 from the LPD, 3 from chemotherapy toxicity, and 2 after allogeneic myeloablative SCT. These patients were treated in a range of centers over a long period of time, before the availability of rituximab, RIC SCT, preemptive EBV PCR screening, and the use of EBV CTLs.

The prolonged period of profound immunosuppression associated with RIC SCT requires vigilance and screening for rising EBV loads after transplantation. Delayed development of EBV CTLs after SCT is associated with increased risk of EBV reactivation and PTLD after conventional-intensity conditioning SCT, and has been shown to occur even later in RIC SCT. In the RIC setting, in vivo use of alemtuzumab contributes to the prolonged immunodeficiency after SCT and is associated with a significant risk of EBV reactivation. PTLD can be avoided by using rituximab pre-emptively in such high-risk patients. The 3 patients described here received pre-emptive rituximab, and none developed PTLD.

The use of EBV-specific CTLs has been shown to be safe and efficacious in the SCT setting, both prophylactically and for the treatment of established PTLD. There are disadvantages with this approach. It takes 8 to 10 weeks to generate CTLs. Furthermore, in the context of established PTLD, localized inflammatory reactions and necrosis may occur. The safest use of EBV CTLs in patients with PID who have pre-existing EBV-LPD undergoing SCT is therefore prophylactic, as was the case for 3 of the patients here. One patient with a rising EBV load after RIC transplantation for XLP was successfully treated using a booster infusion of donor CD34+ cells. Although donor CD34+ cells may be available more readily than ex vivo manufactured EBV CTLs, the time required for CD34+ cell engraftment and subsequent in vivo EBV CTL reconstitution may counter this benefit. The 3 patients who received prophylactic EBV CTLs in this series all remained asymptomatic. Although it is not possible to relate the peak EBV viral loads to clinical disease manifestations in this series, this pre-emptive approach appears safe and efficacious, even in this particularly high-risk population.

The initial engraftment results reported here reflect the previous experience of this group with RIC SCT. It has previously been reported that a loss of full chimerism occurs in some recipients of unrelated donor (UD) grafts after RIC SCT over the course of the first year. Only 1 (14%) of 7 patients reported here had a fall from full-donor chimerism, a lower proportion than that seen in the UD RIC series. However, given the small number of patients reported here, this difference may be of no significance.

Table 3. Clinical and immunologic outcomes of hematopoetic SCT in patients with primary immunodeficiency/immunodysregulatory syndromes complicated by LPD

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Follow-up after BMT, y</th>
<th>Latest immunity</th>
<th>Required Ig replacement</th>
<th>Latest chimerism (mononuclear cells)</th>
<th>Latest chimerism (granulocytes)</th>
<th>Overall outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Undefined CID</td>
<td>7.3</td>
<td>Normal PHA and LSS. Low IgA. Poor Ab responses.</td>
<td>Yes</td>
<td>Mixed high-level</td>
<td>Mixed low-level</td>
<td>Alive and well.</td>
</tr>
<tr>
<td>2</td>
<td>WAS</td>
<td>5.4</td>
<td>Normal PHA response, LSS and Ig. Poor pneumococcal response.</td>
<td>Yes</td>
<td>Full</td>
<td>Full</td>
<td>Alive. Recurrent infections, including pneumococcal sepsis. Improved on restarting IVIG.</td>
</tr>
<tr>
<td>3</td>
<td>IE</td>
<td>5.3</td>
<td>Normal PHA response, LSS, Ig, and Ab responses.</td>
<td>No</td>
<td>Mixed high-level</td>
<td>Mixed high-level</td>
<td>Alive and well.</td>
</tr>
<tr>
<td>4</td>
<td>Undefined CID</td>
<td>5.2</td>
<td>Normal PHA response, LSS, Ig, and Ab responses.</td>
<td>No</td>
<td>Full</td>
<td>Full</td>
<td>Alive and well.</td>
</tr>
<tr>
<td>5</td>
<td>ALPS</td>
<td>3.2</td>
<td>Normal PHA response, LSS, Ig, and Ab responses.</td>
<td>No</td>
<td>Full</td>
<td>Full</td>
<td>Alive and well.</td>
</tr>
<tr>
<td>6</td>
<td>CHH</td>
<td>2.1</td>
<td>Normal PHA response, LSS, Ig, and Ab responses.</td>
<td>No</td>
<td>Full</td>
<td>Full</td>
<td>Alive and well.</td>
</tr>
<tr>
<td>7</td>
<td>XLP</td>
<td>1.4</td>
<td>Normal PHA response, LSS and Ig.</td>
<td>No</td>
<td>Full</td>
<td>Full</td>
<td>Alive and well.</td>
</tr>
<tr>
<td>8</td>
<td>DALD</td>
<td>1.0</td>
<td>Normal PHA response. Low B and CD4 cells.</td>
<td>No</td>
<td>Full</td>
<td>Full</td>
<td>Alive and well.</td>
</tr>
</tbody>
</table>

LSS indicates lymphocyte subsets; PHA, proliferative response to phytohemagglutinin; and Ig, immunoglobulin level.

*Antibody responses not yet assessed.
Avoidance of RIC SCT has been suggested in transplantation for conditions such as XLP in view of the significant risks of PTLD after RIC. However, this risk must be offset against the conditioning-related organ toxicity and late effects of conventional-intensity conditioning. With the approach to EBV surveillance and pre-emptive therapy already described, our results show that it is possible to undertake RIC SCT in patients with primary immunodeficiency or immunodysregulatory disorders, even in the presence of pre-existing LPD.

Acknowledgments

The authors are grateful to Prof Helen Heslop, Prof Chiana Rooney and colleagues at the Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas, for generation and supply of ERV-specific cytotoxic T-cells.

References


Authorship

Contribution: J.C. wrote the manuscript and cared for some patients; J.H. drafted initial patient reports; N.S. provided histopathological input; D.C. provided virological input; P.V., P.A., E.G.D., H.B.G., C.C., A.J. and K.R. designed the therapeutic approach to and managed the care of the patients; and E.G.D. oversaw the writing of the manuscript. E.G.D. and P.V. are joint senior authors.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: E. Graham Davies, Department of Clinical Immunology, Great Ormond St Hospital, Great Ormond St, London, WC1N 3JH, United Kingdom; e-mail: daviegl1@gosh.nhs.uk.
Successful treatment of lymphoproliferative disease complicating primary immunodeficiency/immunodysregulatory disorders with reduced-intensity allogeneic stem-cell transplantation