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

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ABSTRACT

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 haematopoietic stem cell transplantation (SCT) was the only cure for the underlying PID, with a high risk of developing post-transplant complications including recurrent lymphoproliferative disease.

We describe eight patients with a range of PID and immunodysregulatory syndromes complicated by LPD. Following initial treatment of the LPD (including the use of anti-CD20 monoclonal antibody rituximab in six of the patients), all patients underwent reduced intensity conditioned (RIC) SCT with prospective monitoring for EBV-viraemia. After transplant, three received rituximab, and three patients received prophylactic EBV-specific cytotoxic T-lymphocytes. Only one patient developed recurrent LPD post-transplant, which responded to rituximab. All transplanted patients survive free of LPD and cured of their PID, at median follow-up of four years (range one to seven years). With careful monitoring and pre-emptive therapy, we advocate this RIC SCT approach to PID patients with pre-existing EBV-LPD.
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 extra-nodal, B-cell in origin and driven by EBV\(^1\). Typical predisposing PIDs include Wiskott-Aldrich syndrome, ataxia telangiectasia, X-linked lymphoproliferative syndrome, common variable immunodeficiency, and hyper-IgM syndrome\(^2\text{-}^4\).

Historically, the outcome of PID-LPD was very poor, with reported mortality rates nearing 70% where the disease was unresponsive to conventional chemotherapy\(^5\). Such aggressive disease was associated with poor T-cell function, and not to any particular histopathological characteristic aspect of the LPD. Where individuals with PID survived LPD, myeloablative haematopoietic 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 transplant–related mortality for such patients. Furthermore, the very high risk of developing post-transplant lymphoproliferative disease (PTLD) would often preclude SCT.

Several recent advances have made transplantation for PID possible in patients with LPD. Organ-toxic chemotherapeutic regimes 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\(^6\), although recent reports have suggested that RIC SCT in this group may be associated with an increased risk of PTLD\(^7\). Similar RIC regimes have been used to treat adults with LPD arising \textit{de novo}\(^8\) suggesting that myeloablative regimes may not be necessary to control these diseases. Following SCT, the combination of molecular screening for EBV viraemia and prophylactic/pre-emptive therapy with rituximab\(^9\) and EBV-specific CTLs significantly reduces the risk of the development PTLD\(^10\).

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

During the period 1999-2006, eight children presented with LPD complicating PID or immunodysregulatory syndromes at this hospital. Their details are displayed in Table 1. Five patients had primary immunodeficiencies, the other three 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 cases showed evidence of EBV by *in situ* hybridization for EBV-encoded RNA (EBER). Biopsies in two cases showed no evidence that the LPD was EBV-driven.

LPD in five out of six patients responded to chemotherapy, the other (Patient 3) requiring rituximab to control disease. Two patients relapsed following chemotherapy; one relapsing twice (Patient 5). Patients 1 and 5 were maintained on weekly rituximab into transplant. In total, six patients received rituximab prior to transplant to treat their LPD.

All eight patients received non-myeloablative 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 fludarabine 150mg/m² (in 5 divided doses), melphalan 140mg/m² and alemtuzumab 1mg/kg (in 5 divided doses), with CSA as GVHD prophylaxis. Two 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. Two patients with previous cryptosporidial disease also received azithromycin and paromomycin.

As BMT was undertaken to cure both the underlying immunological condition as well as the secondary LPD, cure was defined to include resolution of both problems as judged by clinical and immunological parameters. Patients were monitored following transplantation with regular assessment of immune function and chimerism, as described previously.

Patients 1-4, treated prior to October 2003, were screened for EBV viraemia 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 semi-quantitative assay to determine viral load was performed using serial dilutions of patient plasma. For patients 5-8 screening was performed with real-time quantitative PCR using the whole blood. Patients were closely monitored for symptoms attributable to EBV and PTLD. Those with EBV viraemia were categorized as either (1) asymptomatic, (2) symptomatic viraemia (fever for which no other cause could be identified) or (3) PTLD.

Rituximab was used at doses of 375mg/m² on a weekly basis in patients with rising EBV viraemia, even in the absence of symptoms. Polyclonal EBV-specific cytotoxic T
lymphocytes (CTLs) were generated \textit{ex vivo} by repetitive stimulation of donor T-cells from sero-positive donors with EBV-transformed autologous lymphoblastoid cell lines\textsuperscript{15}. 
RESULTS

The incidence, manifestations and treatment of post-SCT EBV viraemia in the eight transplanted patients are shown in Table 2. Patient 1 went into transplant with EBV viraemia associated with a fever, which settled with five weekly doses of rituximab.

Six patients of the remaining seven patients developed EBV viraemia following transplantation, of whom five remained asymptomatic. Onset of viraemia was at a median of 57 days post-transplant (range 31 to 141 days). Patient 2 developed a viral load of 100,000 copies per ml. He remained asymptomatic but received pre-emptive treatment with two doses of rituximab along with a reduction in immunosuppression. He later received prophylactic CTLs. Patients 3 and 7 also received prophylactic EBV-CTLs. Although both developed asymptomatic viraemia this did not require pre-emptive Rituximab and resolved spontaneously. Patient 5 developed a low level viraemia but did not receive pre-emptive therapy, and remained asymptomatic.

Two patients developed symptomatic EBV disease following transplantation. Patient 6 developed febrile viraemia, which settled after three doses of rituximab. Patient 4 was the only patient to develop PTLD. At 31 days post-transplant, she developed fever, associated with a rash, cervical lymphadenopathy and a hepatic lesion detected on ultrasound imaging. Biopsy was not performed. This was associated with a rise in EBV
load to 10,000 copies/ml. The symptoms and viral load settled following three doses of rituximab and reduction in immunosuppression.

The highest viral load amongst patients not receiving rituximab or EBV-CTLs was 50,000 copies/ml.

Three patients also developed CMV viraemia, one with retinitis requiring a ganciclovir implant. A further patient had retinitis due to VZV.

Of the two patients who had a reduction in immunosuppression to treat EBV, one (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 four years (range one to seven years) (see Table 3). All patients survived, and are currently clinically well. Seven patients had full donor chimerism at initial engraftment in both lineages. In Patient 3, this dropped to high-level mixed chimerism by one year post-transplant, but has remained stable at that level since. Patient 1 achieved high-level mixed chimerism at initial engraftment and this has remained stable since.

Five patients have normal immunological competence, and six patients no longer require replacement immunoglobulin. Patient 2 has poor antibody responses and following 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 seven years post transplant. Patient 8 has a normal PHA
response, but low B- and CD4 T-cells at just under one year following transplant. For Patient 3 who suffered from intractable enterocolitis of infancy, 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\textsuperscript{16,17}, ALPS\textsuperscript{18} and DALD\textsuperscript{19}. Intractable enterocolitis of infancy (IE) is a rare immunodysregulatory syndrome presenting in the neonatal period with pan-enteritis due to an unknown immunological disorder, with a significant risk of developing LPD\textsuperscript{20}. In this series of pre-transplant PID-LPD, five cases had evidence of EBV infection driving the process against a background of abnormal immunity. In the two cases without evidence of EBV, LPD is likely to be attributable solely to impaired immune control.

LPD associated with primary immunodeficiencies represent a heterogeneous pathological category and 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 commonest 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 since in many cases EBV expression can be detected by in situ hybridisation, as was the case with at least one of the patients with Hodgkin disease here\textsuperscript{21}. 
Initial studies suggested that polymorphic PTLD could be monoclonal or polyclonal whereas the majority of monomorphic PTLD are monoclonal. However, molecular analysis reveals that virtually all cases of both polymorphic and monomorphic PTLD are monoclonal. Thus, the assessment of clonality by molecular techniques does not add significant clinically important prognostic information.22

The majority of the LPDs in the setting of primary immunodeficiency / immunodysregulation are aggressive, and the prognosis appears to be related to both the specific underlying immune disorder in addition to the specific subtype of lymphoproliferation. Such cases are generally histopathologically reported according to their phenotype and although precursor lesions have been reported in primary immunodeficiencies, the distinct categories of early lesions, polymorphic and monomorphic PTLD used in the post-transplant setting may not be directly applicable in this setting although are commonly used.22

The largest previous report of the outcome of LPD in the PID setting described 12 cases, with similar predominance of large B-cell lymphoma. Nine of these 12 patients died, four from the LPD, three from chemotherapy toxicity, and two following allogeneic myeloablative SCT. These patients were treated in a range of centres over a long period of time, prior to the availability of rituximab, RIC SCT, pre-emptive 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 post-transplant. Delayed development of EBV-CTL after SCT is associated with increased risk of EBV reactivation and PTLD following conventional intensity conditioned 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 post-SCT and is associated with a significant risk of EBV reactivation. PTLD can be avoided by using rituximab preemptively in such high risk patients. Three patients described here received preemptive 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 8-10 weeks to generate CTLs. Furthermore, in the context of established PTLD localised inflammatory reactions and necrosis may occur. The safest use of EBV-CTLs in PID patients with pre-existing EBV-LPD undergoing SCT is therefore prophylactic, as was the case for three of the patients here. One case of rising EBV load after RIC transplantation for XLP was successfully treated using a booster infusion of donor CD34+ cells. Whilst 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 three 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 following RIC SCT over the course of the first year. Only one of seven patients (14%) reported here had a loss in full donor chimerism, lower than that seen in the UD RIC series. However, given the small number of patients reported here, this difference may be of no significance.

Avoidance of RIC SCT has been suggested in the transplantation of conditions such as XLP in view of the significant risks of PTLD following 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 described above, 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.
<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Immunological abnormality</th>
<th>Age at LPD</th>
<th>LPD Clinical</th>
<th>LPD Histology</th>
<th>EBV-ISH (EBER)</th>
<th>LPD Therapy</th>
<th>EBV load at start of transplant</th>
<th>Therapy at time of BMT</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Femal</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 x4</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>COPx4, followed by rituximab</td>
<td>Not detected</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Femal</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>ChlVPP x6; Local recurrence after 2 months, 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% DNT-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 x6; 2nd relapse (Stage IV disease): Rx ifosfamide/ Cisplatinum/ Etoposide COP, followed by rituximab; IT MTX/steroids</td>
<td>Not detected</td>
<td>Weekly rituximab</td>
</tr>
<tr>
<td>6</td>
<td>Femal</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, surgical resection, COPADMx2</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 tumour complicated by perforation</td>
<td>Monomorphic LPD - DLBCL</td>
<td>-</td>
<td>COP</td>
<td>Not detected</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>Femal</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>
Legend for Table 1

Details of patients with primary immunodeficiency / immunodysregulatory syndromes complicated by lymphoproliferative disease undergoing haematopoetic stem cell transplantation. (EBV-ISH, EBV in situ hybridization; EBER, EBV-encoded RNA; CID, combined immunodeficiency manifest as lymphopenia, poor mitogen responses, hypogammaglobulinaemia and recurrent infections; WAS, mutation confirmed Wiskott-Aldrich syndrome; IE, intractable enterocolitis of infancy; ALPS-like, auto-immune lymphoproliferative syndrome without confirmation of genetic mutation; CHH, cartilage-hair hypoplasia; XLP, mutation confirmed X-linked lymphoproliferative disease; DALD, Dianzani auto-immune lymphoproliferative disease; LPD, lymphoproliferative disease; LyG, lymphomatoid granulomatosis; DLBCL, diffuse large B-cell lymphoma; HD, Hodgkin disease; COP, cyclophosphamide / vincristine / prednisolone; ChlVPP, chlorambucil / vincristine / prednisolone / procarbazine; BEAM, carmustine / etoposide / cytarabine / melphalan; DXT, radiotherapy; ABVD, adriamycin / bleomycin / vincristine / dacarbazine; MTX, methotrexate; COPADM, cyclophosphamide / vincristine / prednisolone / adriamicin, methotrexate; DNT, double-negative T-cells).

*Previously reported35.
<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Age at BMT</th>
<th>Type BMT</th>
<th>Conditioning</th>
<th>GVHD Prophylaxis</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 viraemia</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>
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<tbody>
<tr>
<td>1</td>
<td>Undefined CID</td>
<td>13</td>
<td>MSD PBSCT</td>
<td>TBI 300cGy #1</td>
<td>CSA/MMF</td>
<td>Mixed (high level)</td>
<td>Mixed (high level)</td>
<td>Grade 1 skin</td>
<td>No</td>
<td>Pre-BMT</td>
<td>17900²</td>
<td>Rituximab continued from prior to transplant</td>
<td>Fever but no PTLD</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>CMV retinitis (Implant); Gastrointestinal obstruction due to adhesions</td>
</tr>
<tr>
<td>2</td>
<td>WAS</td>
<td>18</td>
<td>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>100000³</td>
<td>Rituximab x2</td>
<td>Asymptomatic</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>Crypto-sporidial diarrhoea; Pleural effusions (7th cell injury)</td>
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<tr>
<td>3</td>
<td>IE</td>
<td>6</td>
<td>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>10000³</td>
<td>EBV-CTLs</td>
<td>Asymptomatic</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>None</td>
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<tr>
<td>4</td>
<td>Undefined CID</td>
<td>4</td>
<td>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>10000³</td>
<td>No</td>
<td>PTLD</td>
<td>Liver lesions, cervical lymph nodes, fever, rash</td>
<td>Rituximab x3</td>
<td>Full resolution</td>
<td>VZV retinitis</td>
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<tr>
<td>5</td>
<td>ALPS</td>
<td>8</td>
<td>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>5000²</td>
<td>No</td>
<td>Asymptomatic</td>
<td>None</td>
<td>N/A</td>
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<td>CHH</td>
<td>11</td>
<td>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>27000²</td>
<td>Rituximab</td>
<td>Fever but no PTLD</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>Pulmonary aspergillosis</td>
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<tr>
<td>7</td>
<td>XLP</td>
<td>12</td>
<td>1C-MMUD PBSCT</td>
<td>Camp/Flu/Melph</td>
<td>CSA/MMF</td>
<td>Full</td>
<td>Full</td>
<td>No</td>
<td>No</td>
<td>D141</td>
<td>50000²</td>
<td>EBV-CTLs</td>
<td>Asymptomatic</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>Adenoviraeemia; Non-convulsive seizures; Pulmonary fungal infection</td>
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<tr>
<td>8</td>
<td>DALD</td>
<td>7</td>
<td>1C-MMUD BMT</td>
<td>Camp/Flu/Melph</td>
<td>CSA/MMF</td>
<td>Full</td>
<td>Full</td>
<td>Grade 1 skin</td>
<td>No</td>
<td>Never detected</td>
<td>N/A</td>
<td>N/A</td>
<td>Asymptomatic</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>CMV viraemia</td>
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</tbody>
</table>
Legend for Table 2

Details of haematopoietic stem cell transplantation in patients with primary immunodeficiency / immunodysregulatory syndromes complicated by lymphoproliferative disease. Maximum EBV load measured by either 1semi-quantitative PCR or 2quantitative PCR (see text for methods). (CID, combined immunodeficiency; WAS, Wiskott-Aldrich syndrome; IE, intractable enterocolitis of infancy; ALPS, auto-immune lymphoproliferative syndrome; CHH, cartilage-hair hypoplasia; XLP, X-linked lymphoproliferative disease; DALD, Dianzani auto-immune lymphoproliferative disease; MSD, matched sibling donor, MUD, matched unrelated donor; MFD, matched family donor; 1C-MMUD, 1C-antigen mismatched unrelated donor; PBSCT, peripheral blood stem cell transplant; BMT, bone marrow transplant; TBI, total body irradiation; Camp, alemtuzumab 1mg/kg; flu, fludarabine 150mg/m², Melph, melphalan 140mg/m²; GVHD, graft-versus-host disease; CSA, cyclosporin A; MMF, mycophenolate mofetil; CTLs, cytotoxic T-lymphocytes; PTLD, post-transplant lymphoproliferative disease; CMV, cytomegalovirus; VZV, varicella-zoster virus; GCV, ganciclovir; N/A, not applicable).
Table 3

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Follow-up post-BMT (years)</th>
<th>Latest immunology</th>
<th>Requiring immunoglobulin replacement</th>
<th>Latest chimerism (mononuclear cells)</th>
<th>Latest chimerism (granulocytes)</th>
<th>Overall outcome</th>
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<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>
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<tr>
<td>2</td>
<td>WAS</td>
<td>5.4</td>
<td>Normal PHA response, LSS and Igs. Poor pneumococcal response</td>
<td>Yes</td>
<td>Full</td>
<td>Full</td>
<td>Alive. Recurrent infection 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, Igs 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, Igs 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, Igs 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, Igs 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 Igs.*</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>
Legend for Table 3

Clinical and immunological outcomes of haematopoetic stem cell transplantation in patients with primary immunodeficiency / immunodysregulatory syndromes complicated by lymphoproliferative disease.

(CID, combined immunodeficiency; WAS, Wiskott-Aldrich syndrome; IE, intractable enterocolitis of infancy; ALPS, auto-immune lymphoproliferative syndrome; CHH, cartilage-hair hypoplasia; XLP, X-linked lymphoproliferative disease; DALD, Dianzani auto-immune lymphoproliferative disease; LSS, lymphocyte subsets; PHA, proliferative response to phytohaemagglutinin). Igs – Immunoglobulin levels; Ab response – antibody response to vaccines

+ Except for low IgA level    * Ab responses not yet assessed
Reference List


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35. Sebire NJ, Haselden S, Malone M, Davies EG, Ramsay AD. Isolated EBV lymphoproliferative disease in a child with Wiskott-Aldrich syndrome manifesting as
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