T-Cell–Depleted Autologous Bone Marrow Transplantation Therapy: Analysis of Immune Deficiency and Late Complications

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Fourteen patients with T-cell–derived leukemia and lymphoma underwent high-dose chemoradiotherapy and anti-T-cell monoclonal antibody-treated autologous bone marrow transplantation (ABMT). All patients were either in sensitive relapse or had adverse prognostic features, and five patients had a history of bone marrow involvement with disease. Patients received a median of 2 (1 to 3) prior chemotherapy regimens; 10 patients received local radiotherapy. After high-dose ablative therapy, greater than 500/mm^3 granulocytes and greater than 20,000 untransfused platelets/mm^3 were noted at a median of 23 (13 to 48) and 26 (15 to 43) days post-ABMT, respectively. Natural killer (NK) cells, T cells (predominantly T8+), and monocytes were noted within the first 1 to 2 months post-ABMT, as seen in other series. Disease-free survival was a median of 10.1 months, 5.9 months for patients with T acute lymphoblastic leukemia or lymphoblastic lymphoma and 25.6 months for patients with T non-Hodgkin’s lymphoma (NHL). Toxicities were common and severe. Thirty-six percent of patients developed bacteremias early post-BMT. Late complications included a skin rash consistent with graft versus host disease; infections with Herpes zoster, hepatitis, and Pneumocystis carinii; and the development of Epstein-Barr virus associated lymphoproliferative syndrome. Our findings suggest that patients who have undergone T-depleted ABMT have a profound immunodeficiency not reflected in the phenotypic reconstitution of the T and NK cells. Characterization of the functional deficiency may facilitate the development of methods to reduce the long-term toxicity of ABMT in these patients.

SEVERAL CLINICAL and laboratory features (ie, age, tumor burden, and LDH level) appear to predict for survival of patients with diffuse large cell lymphoma (DLH), lymphoblastic lymphoma (LL), and acute lymphoblastic leukemia (ALL). In contrast, the prognostic significance of the immunophenotype in nonHodgkin’s lymphoma (NHL) has been controversial. Although some investigators have reported equivalent survival of similarly treated patients with B- and T-cell NHL, others have reported either shorter or longer survival of patients with T-NHL than those with B-NHL. This variability may reflect heterogeneity in the biology of B versus T lineage NHL, phenotypic methods used, and/or treatment programs utilized. However, it is clear that relapsed NHL of both B- and T-cell origin respond poorly to salvage chemotherapy programs.

High-dose combination chemotherapy with or without radiotherapy and autologous bone marrow transplantation (ABMT) have now been demonstrated to achieve long-term disease-free survival in 25% to 60% patients with NHL in sensitive relapse in patients with either relapsed or high-risk T-cell ALL, LL, and NHL with high-dose chemoradiotherapy and anti-T-cell MoAb-purged ABMT. All patients had sensitive disease and good performance status at the time of transplantation. This series included patients with a prior history of bone marrow involvement and/or extranodal disease. Disease-free survival was a median of 10.1 months, 5.9 months for patients with T-ALL or T-LL and 25.6 months for patients with T-NHL. Although the acute toxicities were similar to those observed in previous studies using cyclophosphamide and total body irradiation ablative therapy, late complications have been more common and include graft-versus-host disease; infections with pneumocystis carinii pneumonia, Herpes zoster, and hepatitis; as well as Epstein-Barr virus-related lymphoproliferative syndromes (EBV-LPS). This high frequency of complications (fatal in three patients) is in marked contrast to the low treatment-related mortality noted in similarly treated patients with B-NHL reported to date.

In this study, we report the results of treatment of 14 patients with either relapsed or high-risk T-cell ALL, LL, and NHL with high-dose chemoradiotherapy and anti-T-cell MoAb-purged ABMT. All patients had sensitive disease and good performance status at the time of transplantation. This series included patients with a prior history of bone marrow involvement and/or extranodal disease. Disease-free survival was a median of 10.1 months, 5.9 months for patients with T-ALL or T-LL and 25.6 months for patients with T-NHL. Although the acute toxicities were similar to those observed in previous studies using cyclophosphamide and total body irradiation ablative therapy, late complications have been more common and include graft-versus-host disease; infections with pneumocystis carinii pneumonia, Herpes zoster, and hepatitis; as well as Epstein-Barr virus-related lymphoproliferative syndromes (EBV-LPS). This high frequency of complications (fatal in three patients) is in marked contrast to the low treatment-related mortality noted in similarly treated patients with B-NHL reported to date.

MATERIALS AND METHODS

Selection of patients and treatment protocol. Patients were eligible for study if they were less than 65 years old and had either T-NHL, T-ALL, or T-LL. Tumor cells expressed T-cell–restricted and associated Ags by indirect immunofluorescence and flow cytometric analysis, or immunoperoxidase staining. Patients with
Patients with T-ALL had relapsed after standard chemotherapeutic regimens or had responded to conventional therapy, but had features predictive of poor prognosis. Patients with T-ALL had relapsed after conventional therapy. For all patients, a minimal disease status had to be attained through chemotherapy, radiotherapy, or both before ABMT. This status was defined as lymph nodal mass less than 2 cm in its greatest diameter, and histologic evidence of bone marrow involvement of 5% or less of the intratrabecular space as determined by iliac crest biopsy. Additional criteria for entry included the absence of comorbid disease of the heart, kidney, lung, and liver, and a Karnofsky score above 80%. Active central nervous system involvement with tumor or any circumstance that would obviate the ability to deliver full-dose total body irradiation (TBI) excluded patients from the protocol. Informed consent was obtained for all patients.

Preparative therapy consisted of cyclophosphamide (Cy), 60 mg/kg of body weight, infused on each of 2 consecutive days before radiotherapy. TBI, 5 to 10 cGy/min, was administered in fractionated doses (200 cGy) twice daily on 3 consecutive days (total of 1,200 cGy). Within 18 hours of the completion of radiotherapy, cryopreserved bone marrow that had been treated previously in vitro with MoAbs and rabbit complement was thawed rapidly and reinfused through a central venous catheter.

Collection, processing, and infusion of marrow. Bone marrow was obtained, treated in vitro with MoAbs and rabbit complement, and cryopreserved within 4 weeks of its use in transplantation. The bone marrow cells were treated with MoAbs directed against antigens expressed by the tumor cells: anti-T11 (CD2) in 1 patient; anti-T4 (CD4) in 1 patient; anti-T6 (CD5) and anti-T3 (CD3) in 3 patients; anti-T1 and anti-T11 in 1 patient; anti-T4 and anti-T11 in 1 patient; anti-T8 (CD8) and anti-T11 in 1 patient; anti-T3 and anti-T12 (CD6) in 2 patients; anti-T1 (CD7) and anti-T12 (CD6) in 1 patient; anti-CALLA (CD9), anti-T1, and anti-T3 in 1 patient; anti-T1, anti-T3, and anti-T12 in 1 patient; and anti-T4, anti-T5, and anti-T11 in 1 patient. The median number of reinfused cells was $3.9 \times 10^{10}/kg$ (range 2.9 to $25.0 \times 10^{10}/kg$), with 85% to 95% variability as measured by Trypan blue exclusion.

Supportive care. Patients were treated and cared for in reverse isolation rooms until they were discharged. Discharge was permitted if the absolute granulocyte count was stable at greater than 500/mm$^3$ and no fever had occurred in the absence of antibiotics for 24 to 48 hours. Trimethoprim-sulfamethoxazole or ciprofloxacin prophylaxis was started in patients when chemotherapy was initiated, but was stopped if broad spectrum intravenous antibiotics were required. Patients also received prophylactic acyclovir for Herpes simplex infections. There were no acute infections similar to those observed in prior studies using cyclophosphamide and total body irradiation. The major acute toxicity was fever associated with neutropenia. Although 12 patients developed fever, positive blood cultures were obtained in only five patients (Table 2). These were all due to gram-positive organisms (Staphylococcus epidermidis and alpha streptococcus). A single patient developed subclavian thrombosis and thrombophlebitis necessitating removal of Hickman catheter and broad spectrum antibiotic therapy. Severe mucositis and esophagitis was noted in 4 of the 6 patients who underwent mediastinal radiation therapy before ABMT.

Late complications have been common. At 2 months PT for T-ALL, a single patient developed a central pruritic maculopapular rash that progressed to involve the extremities and resolved with only topical hydrocortisone cream. Biopsy showed a poikilodermatous infiltrate with mild epider-
mal maturation dysarray, and basilar dyskeratosis with satellitosis consistent with early acute graft-versus-host disease. Two patients developed *Pneumocystis carinii* pneumonia at 4.8 and 5.7 months PT. Three patients developed dermatomal Herpes zoster at 3, 4.2, and 16.5 months PT, and one patient died in the setting of pneumonitis, positive at 1:1,280 before transplant, was unchanged. Ten months PT the patient died in the setting of pneumonitis, compatible with acute hepatitis, while gram and acid fast stains were negative. Serum CMV antibodies remained positive at 1:2,560, unchanged from that before transplant.

Two patients have developed EBV-LPS. A 27-year-old man with T-LL in remission was treated with Cy (60 mg/kg × 2 days) and TBI (1,200 cGy) followed by infusion of autologous marrow that had been treated in vitro with MoAbs to CD2, CD4, and CD5 plus complement. He developed fever while neutropenic, necessitating broad spectrum antibiotic therapy, but all cultures were negative. He was discharged 22 days PT.

At 42 days PT, when he was readmitted for evaluation of fever and pharyngitis, the results of a physical examination and liver-function testing were normal. The hematocrit was 24% and the white blood cell (WBC) count 4,900/mm³, with 31% neutrophils, 48% lymphocytes, 17% monocytes, 1% eosinophils, and 1% atypical lymphocytes. On day 6 of hospitalization, symptomatic erythematous pharyngitis, left posterior cervical, and right axillary lymphadenopathy were noted. The serum bilirubin level was 2.0 mg/dL, serum aspartate aminotransferase 124 U/L, and serum AP 480 U/L. The patient's serum EBV-VCA immunoglobulin G (IgG) titer was 1:2,560, unchanged from that before transplantation. Cervical lymph node showed a polymorphous infiltrate composed predominantly of IgM-positive CD20-positive B lymphocytes, histiocytes, plasma cells, and immunoblasts, indicative of evolving monoclonal B-lymphocyte proliferation. At least half the lymph node cells showed characteristic staining for EBV nuclear protein 2 (np 2), and at least half the lymph node cells showed characteristic staining for EBV nuclear protein (NP) and EBV-encoded small RNA (EBER). The patient remained

### Table 1. Characteristics of Patients Undergoing MoAb-Purged ABMT

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age*</th>
<th>Sex†</th>
<th>Histology at ABMT§</th>
<th>Previous Sites of Extramedullary Disease</th>
<th>Therapy Before ABMT¶</th>
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<tr>
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<td>52</td>
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<td>2</td>
<td>29</td>
<td>F</td>
<td>LL</td>
<td>Bone marrow, spleen</td>
<td>Dau Lasp OP ITM 6MP M/L; XRT mediatinum; Mit PO ITM; M/L</td>
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<tr>
<td>3</td>
<td>32</td>
<td>F</td>
<td>DLCL</td>
<td>None</td>
<td>m BACOD; ara C; XRT mediatinum</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>IS</td>
<td>Lung</td>
<td>Mit BACOD; MOP L araCE</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>M</td>
<td>DLCL</td>
<td>Skin</td>
<td>CHOP; CHOP; XRT skin</td>
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<tr>
<td>6</td>
<td>43</td>
<td>M</td>
<td>DPDL</td>
<td>Bone marrow</td>
<td>CHOP; XRT inguinal nodes; MOP-LaraCE</td>
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<td>F</td>
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<td>Lung, pleura</td>
<td>CHOP; SRT mediatinum; m BACOD</td>
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<tr>
<td>8</td>
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<td>LL</td>
<td>Pleura</td>
<td>CHOP; XRT craniospinal axis; M/L/ITM</td>
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<td>m BACOD; XRT mediatinum; ara C</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>M</td>
<td>ALL</td>
<td>Bone marrow, skin</td>
<td>Dau Lasp OP M 6MP; Dau O Prm; Dau DP M/L</td>
</tr>
<tr>
<td>11</td>
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<td>Bone marrow, spleen</td>
<td>CHOP; DACis</td>
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<tr>
<td>12</td>
<td>31</td>
<td>M</td>
<td>ALL</td>
<td>Bone marrow, kidney</td>
<td>MOP; Dau OPML; XRT craniospinal axis</td>
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<td>28</td>
<td>F</td>
<td>DLCL</td>
<td></td>
<td>m BACOD; DA Cis; XRT mediatinum</td>
</tr>
</tbody>
</table>

*Years.
†Male (M) or female (F).
‡Immunoblastic sarcoma (IS), lymphoblastic lymphoma (LL), diffuse large cell lymphoma (DLCL), diffuse poorly differentiated lymphocytic lymphoma (DPDL), acute lymphoblastic leukemia (ALL).
¶Low-dose methotrexate (m), bleomycin (B), adriamycin (A), cyclophosphamide (C), Oncovin (O), dexamethasone (D), daunorubicin (Dau), L-asparaginase (Lasp), prednisone (P), radiation therapy (XRT), intrathecal methotrexate (ITM), 6 mercaptopurine (6MP), high-dose methotrexate (M), leucovorin (L), mitoxantrone (Mit), cytosine arabinoside (araC), etoposide (E), hydroxydaunorubicin (H), cis-platinum (Cis).
febrile, with worsening liver function and associated renal failure, and died on day 20 of hospitalization (61 days PT). At postmortem examination, the common bile duct was found to be completely obstructed by enlarged periampullary lymph nodes. The lymph nodes showed marked hemorrhage and lymphocyte depletion with scattered immunoblasts. No lymphoma was found.

A 25-year-old woman with T-cell DHL in second remission underwent ABMT using marrow depleted with MoAbs to CD5 and CD6. Before ablative Cy (60 mg/kg x 2 days) and TBI (1,200 cGy), she received 4,500 cGy to the mediastinum, a site of bulk disease. After ablative therapy, she developed the expected profound neutropenia and a mild mucositis, but remained afebrile. Her first granulocytes returned on day 10, and by day 29 PT greater than 500 granulocytes/mm³ were noted. Liver function tests remained entirely normal until day 19 PT when SGOT was 77 U/L, ALT 141 U/L, and AP 72 U/L, with normal total and direct bilirubins. Thirty-one days PT diffuse anterior and posterior cervical adenopathy without other adenopathy or organomegaly was noted. WBC count was 1,400/mm³ with 30% granulocytes, 36% lymphocytes, and 10% monocytes, and liver function tests were normal except for an LDH of 720 U/L (normal 293 to 639 U/L). Serologic and culture evaluation for toxoplasmosis, CMV, and Herpes simplex virus were negative. Cervical node biopsy showed large cell immunoblastic sarcoma of IgM, CD20 positive B-cell type. EBV np2 and LMP were both positive, consistent with the view that this represented an EBV-LPS. EBV-VCA was 3.0 (low positive), unchanged from that before ABMT. The absolute neutrophil count decreased, atypical lymphocytosis increased (WBC count 1,200/mm³, 26% polys and 24% atypical lymphocytes), and 30% circulating CD20 positive cells were evident. Due to low grade fever on day 36 PT, broad spectrum antibiotics were begun. Therapy for EBV-LPS was instituted with IV gammaglobulin (400 mg/kg/d on days 1 through 3 and then weekly), a 2 interferon (3 x 10⁶ U/m² subcutaneously daily), and acyclovir (12.5 mg/kg body weight intravenously every 8 hours). Increasing cervical and auricular tender adenopathy was noted bilaterally, with persistent low-grade fevers and new elevation of liver function tests (LDH 837 U/L, AP 167 U/L, with TB 2.9 mg/dL, and DB 2.1 mg/dL). CT scan of the abdomen and pelvis showed no evidence of adenopathy or hepatosplenomegaly, and chest x-ray demonstrated no increase in mediastinal adenopathy. Although her liver function tests worsened
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(TB 9.8 mg/dL, DB 9.0 mg/dL, SGOT 87 U/L, LDH 1163 U/L, and AP 151 U/L), decreased tenderness and shrinkage of her neck adenopathy with an associated decrease in atypical lymphocytosis was noted by day 41 PT. On day 44 PT, no adenopathy was present and WBC count was 2,800/μL, and AP 151 U/L), decreased tenderness and shrinkage showed no circulating CD20 positive cells. On day 45 PT, TB 9.8 mg/dL, DB 3.3 mg/dL, AP 183 U/L, SGOT 87 U/L, and LDH 863 U/L. Repeat phenotyping of her PBMCs was changed to an every other day schedule, and gammaglobulin was administered weekly. She was discharged 51 days PT but remained pancytopenic, requiring weekly transfusions of both RBCs and platelets.

Subsequent hospitalizations were required for gram-positive (enterococcus) septicemia at day 101 PT, S. epidermidis septicemia at day 145 PT, and P. carinii pneumonia, from which she died on day 202 PT. No lymphoma was found at postmortem examination.

**Therapeutic results.** Five of the 14 patients have relapsed at a median of 5.9 (5.3 to 25.6) months PT; 4 of these 5 patients have died at a median of 10.2 (7.2 to 13.5) months PT. As noted above, there were 3 toxic deaths: 1 patient who developed EBV-LPS and died at 2.0 months PT; 1 patient who developed EBV-LPS at 1 month PT and died at 6.6 months PT with P. carinii pneumonia; and a single patient who died with hepatitis at 10.1 months PT. Six patients remain alive and disease-free at a median of 13.3 (7.0 to 39.8) months PT, and one patient who relapsed at 25.6 months PT is alive on therapy at 60.7 months PT.

Median overall survival for all patients was 13.5 months, 7.2 months, and not yet reached for patients with T-ALL/LL and T-NHL, respectively. Disease-free survival was a median of 10.1 months, 5.9 months for patients with T-ALL or T-L and 25.6 months for patients with T-NHL. Although patient numbers are small, disease-free survival in those nine patients without and those five patients with a history of bone marrow involvement appeared to be similar.

Three patients with T-DHL have relapsed, two at sites of prior disease (skin and bone marrow) and one in axillary nodes not previously involved. Two patients with T-ALL demonstrated hematologic relapse in blood and bone marrow. The presence of extranodal disease did not predict for relapse.

**Phenotype analysis of reconstituting PBMCs.** The recovery of T, B, and NK cells early after T-ABMT is depicted in Table 3. NKH1+ cells and CD5+CD3+CD6+ T cells each represented approximately 30% of PBMCs in the first 5 weeks PT. Anti-CD2 MoAb stains both T cells and NK cells and reacted with a median of 55 (22% to 85%) of PBMCs. CD8 Ag positive cells were three times more common than CD4 Ag-staining cells. CD14 Ag-bearing monocytes comprised approximately 20% of PBMCs. These trends persisted at weeks 6 through 12 PT. B cells were largely absent in the first 5 weeks PT, but were present at 3% (0% to 7%) at 6 to 12 weeks PT.

Two patients developed EBV-LPS at 5 and 6 weeks PT; at the time, increased numbers of CD20+ monoclonal B cells (27% and 15%, respectively) were present. Phenotypic examination at 3 weeks PT did not distinguish the patient who developed EBV-LPS at 6 weeks PT from those patients who did not. In addition, EBV-VCA titers before transplant were equivalent in those two patients who developed EBV-LPS and in those 12 patients who did not.

**DISCUSSION**

In this study, we report the results of 14 patients with T-cell lymphoma or leukemia who underwent high-dose chemotherapy and anti-T cell MoAb-treated ABMT. All of these patients were heavily pretreated and had either relapsed or had other adverse prognostic features. At the time of transplant, all patients demonstrated good performance status with a Karnofsky score of 80% or greater and were in CR. Overall disease-free survival was 10.1 months, 5.8 months for patients with T-ALL or LL and 25.6 months for patients with T-NHL. Although the acute toxicities were similar to those observed in prior studies using cyclophosphamide and TBI ablative therapy, late complications have included a skin rash consistent with graft-versus-host disease (GVHD); infections with P. carinii pneumonia, Herpes zoster, and hepatitis; as well as EBV-LPS. Our data suggest that T-depleted ABMT for patients with T-cell leukemia and

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Table 3. Immune Reconstitution After T-Cell-Depleted ABMT

<table>
<thead>
<tr>
<th>Cell Surface Antigen (CD)</th>
<th>Percentage of Cells Expressing Cell Surface Antigen</th>
<th>Weeks 1-5 PT</th>
<th>Weeks 6-12 PT</th>
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<tr>
<td></td>
<td>Pt 1*</td>
<td>Pt 2†</td>
<td>Pt 1*</td>
</tr>
<tr>
<td>T1 (CD5)</td>
<td>15 (9-62)‡</td>
<td>44</td>
<td>24 (5-53)</td>
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<td>T3 (CD3)</td>
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<td>10 (7-21)</td>
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<tr>
<td>B1 (CD20)</td>
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<td>1</td>
<td>3 (0-7)</td>
</tr>
<tr>
<td>Mo1 (CD11b)</td>
<td>43 (22-47)</td>
<td>55</td>
<td>41 (0-57)</td>
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<tr>
<td>Mo2 (CD14)</td>
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<tr>
<td>NKH1 (CD56)</td>
<td>27 (8-64)</td>
<td>31</td>
<td>27 (4-48)</td>
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</table>

*Patient 1 developed EBV-LPS 6 weeks PT.
†Patient 2 developed EBV-LPS 5 weeks PT.
‡Median (range) for patients who did not develop EBV-LPS.
lymphoma has a higher frequency of complications than similarly treated patients with B-NHL.

Our results of disease-free survival in patients with sensitive relapsed T-NHL are similar to those previously reported in other series of NHLs or of only B-NHLs.17-31 In contrast, patients with T-ALL or LL had very short survival. There is no evidence to date, either from this or other studies of NHLs, that purging is necessary. Nonetheless, it is of interest that survival in our study was equivalent for those patients with or without a history of bone marrow involvement. Hematologic engraftment and transfusion requirements were also similar to other reported series.46,67 However, toxicity was markedly increased in our patients.

Infections noted post T-depleted ABMT were mainly those associated with cellular immunodeficiency, namely viral (Herpes zoster, hepatitis, and EBV) and opportunistic (P. carinii) infections. However, it should be noted that 5 of 14 (36%) of patients developed bacteremia, compared with the 16% incidence of bacteremia in 100 recipients of purged ABMT for B-NHL at our institute.29 Two of our patients developed EBV-LPS after T-depleted ABMT, and to our knowledge, are the first such patients to have developed this complication after autologous marrow grafting. These syndromes have been described post-allogeneic BMT, in the settings of GVHD and HLA disparity, T-cell depletion from donor marrow, and MoAb treatment of GVHD.40-51 This complication appears to be rare. Zutter et al32 reported 15 cases of secondary B-cell lymphoproliferative disorders among 2,475 patients who underwent allogeneic BMT in Seattle, WA (0.6%). A more recent report, also from Seattle, documents EBV-related lymphomas in 11 of 2,246 (0.49%) patients who received BMT for leukemia or aplastic anemia.52 In this series, most B-cell lymphomas occurred shortly after exposure to intensive immunosuppression to treat acute GVHD, and often in the setting of an HLA mismatch. Three patients developed EBV-related lymphomas more than 100 days PT, two of whom received grafts with T-cell depletion and one of whom had an HLA mismatched donor. Shapiro et al33 reported EBV-LPS in 6 of 25 (24%), 0 of 47 (0%), 1 of 10 (10%), and 1 of 424 (0.2%) recipients of HLA mismatched T-depleted, HLA matched T-depleted, nondepleted unrelated, and HLA matched nondepleted grafts, respectively. In our experience, we have documented EBV-LPS in 0 of 62 patients with HLA identical sibling donors and 1 of 12 patients with HLA nonidentical sibling donors who received anti-Cd6-depleted allogeneic marrow transplants for hematologic malignancies.34 Although chronic antigenic stimulation from the allograft has been implicated as a contributing factor in the development EBV-LPS after transplantation,35 our cases of EBV-LPS after ABMT suggest that immunosuppression rather than antigenic stimulation may predispose to EBV-LPS. Further support for this hypothesis is the well-documented occurrence of EBV-LPS in immunocompromised hosts; 46,48 i.e., patients with acquired immunodeficiency syndrome,53,54 ataxia telangiectasia,55 severe combined immunodeficiency syndrome,60 organ transplants,61,62 or Hodgkin’s disease.53 Both abnormal humoral responses to antigenic determinants of EBV and defective in vitro cytotoxicity against virus-transformed lymphocytes have been described in the setting of Hodgkin’s disease.64

In those cases of EBV-LPS reported after allogeneic BMT, restriction fragment length polymorphic and cytogenetic analysis of involved tissue has demonstrated some cases of donor and some of recipient origin.56,57 In our cases, the cells are obviously of host origin. In this regard, it was of interest to examine whether there was indication of active EBV infection before ABMT in those patients who developed EBV-LPS post-ABMT. No significant difference in EBV VCA pre-ABMT titers was evident in those patients who did and did not develop EBV-LPS, and titers did not increase in the two patients with the development of EBV-LPS. Given the fact that these patients may be immunosuppressed in a variable pattern, serologic analysis may not be a reliable indication of active infection. EBV has been reported to infect T cells and contribute to lymphomas in selected patients with severe EBV infections.65 Moreover, separate B- and T-cell clones have been defined in a patient’s NHL, suggesting the existence, in some patients, of a transformed lymphocyte-committed stem cell that is capable of generating both T- and B-cell clones.66 In our two patients with EBV-LPS, the original T-cell tumors were not examined for EBV. Nonetheless, immunosuppression of T-depleted marrow recipients appears more likely as the major predisposing factor.

It is interesting to speculate whether the T-depletion of our marrow BMT may account for additional immunosuppression relative to recipients of either unpurged or B-cell–purged ABMT. Our data suggest that the pattern of early immune reconstitution in those two patients who developed EBV-LPS did not significantly differ from those 12 recipients of T-ABMT who did not develop EBV-LPS or from recipients of B-cell purged ABMT at our institution.46,67 In all settings NK cells, T cells (predominately T8+), and monocytes predominate within the first 1 to 2 months PT with few, in any, B cells. This is also the pattern of reconstitution noted after CD6 depleted allogeneic BMT at our institution and allogeneic BMT elsewhere.67,68 The two patients who developed EBV-LPS received marrow depleted with anti-CD5, CD4, and CD2 MoAbs and anti-CD5 and CD6 MoAbs, respectively; they were 2 of 8 patients whose marrows were purged with combinations including MoAbs directed against CD5. Because other patients’ marrows in our series were depleted with these MoAbs before ABMT, it does not appear to be particular depletion techniques that predispose to the development of EBV-LPS. Nonetheless, the high incidence (14%) of EBV-LPS in our series does suggest that T-depletion of marrow using MoAbs and complement does increase the likelihood of EBV-LPS, most likely due to additional immunosuppression. We did not examine T-cell function in general, and more specifically, the ability to respond to EBV-infected autologous target cells.

Treatment of EBV-LPS PT has been problematic. When patients who are on immunosuppressive therapy, such as cyclosporine, develop EBV-LPS, resolution has been described when this immunosuppressive therapy is discontinued.69 Alternatively, stimulation of the immune response
to EBV-transformed cells with interferon α, and treatment with either B-cell MoAbs or cytotoxic therapy has been used to deplete EBV-infected proliferating lymphocytes. Our first patient was treated with high-dose methotrexate, which resulted in marked shrinkage of tumor but did not alter his demise due to progressive hepatic failure. Interestingly, our second patient with EBV-LPS was treated with interferon γ, gammaglobulin, and acyclovir, as described by Shapiro et al., and completely cleared any clinical or laboratory evidence of EBV-LPS. Although this latter treatment regimen resulted in marked shrinkage of tumor but did not alter his course, our patient nonetheless died with P carinii pneumonia, further evidence of underlying and persistent immunodeficiency.

Our study suggests that T-depleted autologous BMT can achieve prolonged disease-free survival in some patients with T-NHL in sensitive relapse. Other preclinical or clinical studies of the depletion of malignant T cells from marrow before ABMT using MoAbs and magnetic immunobeads, MoAb-immunotoxin conjugates, chemotherapy, or combinations of immunologic and pharmacologic approaches, have also been promising. Our 29% 3-year disease-free survival for patients with T-NHL is similar to the 50% probability of disease-free survival at 37.8 months in 100 patients who underwent MoAb-purged ABMT for B-NHL at our institute.

However, our findings suggest that patients who have undergone T-depleted ABMT have a profound immunodeficiency post-BMT that is not reflected in the phenotypic reconstitution of their T and NK cells post-BMT. Further studies of the functional immune deficiency post-BMT are needed to develop methods for reducing the long-term toxicity of ABMT in these diseases.

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T-cell-depleted autologous bone marrow transplantation therapy: analysis of immune deficiency and late complications