Prompt versus preemptive intervention for EBV lymphoproliferative disease


Brief report

Posttransplantation lymphoproliferative disorders (PTLDs) caused by uncontrolled expansion of Epstein-Barr virus (EBV)–infected B cells after hematopoietic stem cell transplantation (HSCT) can be predicted by an increase in EBV DNA in peripheral blood mononuclear cells. We used real-time quantitative polymerase chain reaction (RQ-PCR) analysis to determine whether frequent monitoring of EBV DNA to allow preemptive treatment is truly of value in patients after HSCT. More than 1300 samples from 85 recipients were analyzed. No patient with consistently low EBV DNA levels developed PTLD. Nine patients had a single episode with a high EBV load (more than 4000 EBV copies/μg peripheral blood mononuclear cell [PBMC] DNA), and 16 patients had high EBV loads detected on 2 or more occasions. Only 8 of these developed symptoms consistent with PTLD, and all were promptly and successfully treated with EBV-specific cytotoxic T cells or CD20 monoclonal antibody. Hence, quantitative measurement of EBV DNA may best be used to enable the prompt rather than the preemptive treatment of PTLD. (Blood. 2004;103:3979-3981)

Introduction

For the first year after hematopoietic stem cell transplantation (HSCT), Epstein-Barr virus (EBV)–induced posttransplantation lymphoproliferative disorders (PTLDs) are the most common neoplastic diseases among patients.1 They may occur after any HSCT, but they are more common if donor and recipient are HLA-mismatched or if T-cell depletion is used for graft-versus-host disease (GVHD) prophylaxis.1 The clinical diagnosis of PTLD may be difficult because it is a spectrum of heterogeneous histologic and clinical entities. It may present as an infectious mononucleosis-like illness, with fatigue and lymphadenopathy, or as a febrile illness with leukopenia. Almost all organs may be affected by disease. Because of the progressive nature of PTLD, the key to management may be early or even preemptive treatment with either anti–B-cell monoclonal antibodies2–4 or donor-derived EBV-specific cytotoxic T lymphocytes (CTLs).5–7 Preemptive treatment is feasible because the onset of EBV-associated PTLD is foreshadowed for several weeks by an increase in EBV load (more than 4000 EBV copies/μg peripheral blood mononuclear cell [PBMC] DNA) in the peripheral blood of patients receiving a transplant from an HLA-mismatched family member or an HLA-matched unrelated donor.7–10

The study of HSCT patients has revealed that preemptive intervention with antiviral agents when cytomegalovirus (CMV) DNA levels increase is an effective way to prevent the onset of overt CMV disease, which retains high morbidity and mortality rates.11 Hence, careful monitoring of CMV DNA levels after HSCT reveals a group of patients to whom treatment can be given preemptively with the greatest benefit. We questioned whether a similar strategy was of value in guiding the treatment of patients with EBV reactivation after HSCT, or whether the detection of high EBV DNA levels was better used to confirm clinically overt EBV PTLD and to facilitate prompt rather than preemptive treatment.

We used accurate real-time quantitative polymerase chain reaction (RQ-PCR) amplification in HSCT patients who were receiving a transplant from an unrelated donor or a mismatched family member and who were at high risk for the development of EBV-associated PTLD. We tried to determine whether detecting high EBV DNA levels using this technique was sufficiently sensitive and specific to support preemptive intervention. We also determined the outcome of prompt treatment of established EBV PTLD. Our results suggest that, in contrast to measurements of CMV DNA, EBV DNA levels are best used to confirm diagnoses of EBV PTLD, thereby permitting intervention that is early and effective rather than preemptive but unnecessary.

Study design

Patients

We studied 111 patients who underwent HSCT from closely HLA-matched unrelated donors or HLA-mismatched family members between May 1998 and July 2002 (Table 1).12–13 All patients received fully ablative conditioning regimens that included ATG or alemtuzumab (Campath)12–13 and either unmanipulated marrow or peripheral blood stem cells (PBSCs), a T-cell-depleted product, or a T- and B-cell–depleted product (Table 1). Eighty-five of these 111 patients had EBV that had been monitored on at least 4 occasions and were included in this analysis. The remaining 26...
patients underwent fewer than 4 analyses because of early relapse, death before day 100, or graft failure. In all patients, EBV DNA load was serially monitored every 2 weeks after transplantation.

Quantification of EBV DNA in PBMCs using RQ-PCR

PBMCs were enriched from heparinized blood samples of patients by standard density centrifugation and DNA isolated from PBMCs and quantitated as previously described. For Epstein-Barr viral load measure-

ments, an RQ-PCR assay specific for the highly conserved EBER 1 region of the EBV genome was used as described in detail elsewhere. Generation and adoptive transfer of EBV-specific CTL

EBV-specific CTL were prepared as described in detail elsewhere.

Table 1. Demographics of 85 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Donor</th>
<th>T cell depletion</th>
<th>Symptoms</th>
<th>EBV DNA</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>J31</td>
<td>6 of 6 URD</td>
<td>Ex vivo T-cell depletion</td>
<td>Fever, pneumonia</td>
<td>40 000</td>
<td>CTLs</td>
<td>Symptoms resolved, and EBV DNA returned to normal</td>
</tr>
<tr>
<td>J23</td>
<td>6 of 6 URD</td>
<td>Ex vivo T-cell depletion</td>
<td>Fever</td>
<td>4 000</td>
<td>CTLs and rituximab</td>
<td>Symptoms resolved, and EBV DNA returned to normal</td>
</tr>
<tr>
<td>2110</td>
<td>6 of 6 URD</td>
<td>Ex vivo T-cell depletion</td>
<td>Lymphadenopathy</td>
<td>20 000</td>
<td>Rituximab</td>
<td>Symptoms resolved, and EBV DNA returned to normal</td>
</tr>
<tr>
<td>J28</td>
<td>6 of 6 URD</td>
<td>Ex vivo T-cell depletion</td>
<td>Cough, fever</td>
<td>36 539</td>
<td>CTLs</td>
<td>Symptoms resolved, and EBV DNA decreased but remained above normal for several months</td>
</tr>
<tr>
<td>J180</td>
<td>6 of 6 URD</td>
<td>Ex vivo T- and B-cell depletion</td>
<td>Abdominal pain, after ATG for GVHD</td>
<td>176 009</td>
<td>Rituximab</td>
<td>Symptoms resolved, and EBV DNA returned to normal</td>
</tr>
<tr>
<td>J152</td>
<td>6 of 6 URD</td>
<td>Ex vivo T- and B-cell depletion</td>
<td>Fever</td>
<td>29 807</td>
<td>Rituximab</td>
<td>Symptoms resolved, and EBV DNA returned to normal</td>
</tr>
<tr>
<td>J363</td>
<td>6 of 6 URD</td>
<td>In vivo alemtuzumab</td>
<td>Fever</td>
<td>74 346</td>
<td>Rituximab</td>
<td>Symptoms resolved, and EBV DNA returned to normal</td>
</tr>
<tr>
<td>J366</td>
<td>6 of 6 URD</td>
<td>In vivo alemtuzumab</td>
<td>Fever</td>
<td>103 695</td>
<td>Rituximab</td>
<td>Symptoms resolved, and EBV DNA returned to normal</td>
</tr>
</tbody>
</table>

URD indicates unrelated donor.
Is routine monitoring required?

We and others have previously shown that elevated EBV DNA levels are highly predictive for the development of EBV PTLD in recipients of T cell–depleted transplants.8,9 The inference is that recipients of T cell levels are highly predictive for the development of EBV PTLD in We and others have previously shown that elevated EBV DNA levels after HSCT will allow preemptive treatment of patients before overt EBV PTLD appears. Such a strategy has been beneficial when applied to CMV, another latent herpesvirus that frequently causes disease after HSCT. However, preemptive treatment of CMV is desirable because therapy for established disease still has a high failure rate. Overt EBV PTLD, by contrast, may be more readily amenable to treatment.2,5,15 Moreover, the predictive power of detecting EBV DNA levels higher than 4000 on more than 2 occasions was only 50% in this series, indicating that preemptive treatment would expose half the recipients to unnecessary therapy. Accordingly, we treated patients only when a persistently high EBV DNA level was coupled with clinical symptoms and signs of EBV PTLD. All patients responded completely. We suggest that the most effective way to prevent morbidity and mortality from EBV PTLD after HSCT is to maintain a high index of suspicion for the disease and to confirm a clinical assessment by measuring EBV DNA using accurate RQ-PCR. This approach allows prompt treatment while avoiding needless preemptive intervention.

References

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