Herpes Zoster Infection After Autologous Bone Marrow Transplantation

By Lynn M. Schuchter, John R. Wingard, Steven Piantadosi, William H. Burns, George W. Santos, and Rein Saral

One hundred fifty-three patients who underwent autologous bone marrow transplant (ABMT) were studied retrospectively to determine the frequency, outcome, and risk factors associated with varicella-zoster infections (VZV). Forty-three patients (28%) developed VZV infection after transplant. The median onset of infection was the fifth month, with 91% of cases occurring within the first year. Thirty-three patients (77%) had localized herpes zoster, and ten patients (23%) had varicella. Cutaneous dissemination developed in 15% of patients and probable visceral dissemination developed in 5%. Overall morbidity was 25% and included scarring, alopecia, postherpetic neuralgia, and neurologic dysfunction. There were no deaths from VZV infection. The majority of patients (79%) were treated with intravenous (IV) acyclovir. The only significant risk factor associated with VZV infection was the underlying disease. VZV infection occurred most frequently in patients with Hodgkin's and non-Hodgkin's lymphoma (46%) as compared with patients with leukemia (23%) or solid tumors (9%) (P < .002). The frequency of VZV infection in ABMT patients appears to be comparable to that reported for allogeneic BMT patients and other immunocompromised patients.

A U T O L O G O U S bone marrow transplantation (ABMT) is used increasingly to treat patients with hematologic malignancies and solid tumors. Morbidity and mortality from ABMT is largely due to infectious complications, treatment-related toxicities, and tumor relapse. Varicella zoster virus (VZV) infections are particularly common in patients with malignancies or in patients receiving chemotherapy or immunosuppressive therapy, including ABMT. The frequency of VZV infection in allogeneic BMT recipients ranges from 17% to 50%, making it one of the most common late infections in this patient population. The frequency of VZV infection after ABMT has not been previously reported. We present our experience with VZV infection in 153 patients who underwent ABMT. The purpose of this analysis is to determine the frequency, risk factors, and outcome of VZV infections in ABMT patients.

MATERIALS AND METHODS

Patients. All patients who underwent ABMT between January 1983 and December 1987 at the Johns Hopkins Oncology Center who survived >100 days were included in this analysis. Case identification was retrospective, and information was collected by chart review and contact with referring physicians and/or patients. Follow-up data was collected as of June 1987. Approval was obtained from the Institutional Review Board for these studies. Patients gave written informed consent for blood samples obtained, and the privacy of patients was protected.

Patient management. The methods and technique of marrow transplantation have been previously described. Patients received either busulfan (BU) plus cyclophosphamide (Cy) or Cy and total body irradiation (TBI). Marrow was purged by 4-hydroperoxycyclophosphamide before cryopreservation as described previously.

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Herpes zoster was defined as vesicular skin lesions with a generalized onset and no dermatomal distribution. Visceral dissemination was defined as the subsequent development of six or more skin lesions that did not conform to any dermatomal distribution. Visceral dissemination was considered probable if there were concurrent abnormalities on chest radiograph or liver function tests with compatible clinical signs and symptoms and no other cause was determined. Documented visceral dissemination was defined as recovery of the organism from tissue or demonstration of typical histopathologic changes in tissue specimens. Varicella was defined as the appearance of vesicular skin lesions with a generalized onset and no dermal distribution irrespective of previous VZV infection. Visceral dissemination of varicella was specified as above. Postherpetic neuralgia was defined as dermal pain which persisted beyond 28 days after initial presentation of infection.

To analyze for possible risk factors associated with development of VZV infections, the following data were retrieved: underlying disease, remission status of malignancy, previous radiation therapy, preparative regimen, age, sex, and pretransplant serum VZV antibody titer. The primary statistical endpoints of this study were time to viral infection and time to relapse. Event-time distributions were estimated using the product-limit method. Differences between event-time distributions were tested using the log-rank statistic. The prognostic importance of baseline risk factors for developing viral
infection was assessed in a multivariate proportional-hazards model. For risk factors becoming manifest between transplant and the endpoint, a time-dependent covariate relative-risk regression model was used to assess statistical significance. The association between categorical factors was tested using the chi-square statistic. Differ-
ences between distributions of continuous factors in groups were tested using nonparametric analysis of variance. All P values reported are two-sided.

RESULTS

Patient characteristics. Between January 1983 and December 1987, 213 patients underwent ABMT. Of these, 56 patients were excluded from this analysis because they survived <100 days after BMT. One hundred fifty-seven patients were identified, and follow-up data is available for 153. Four patients were lost to follow-up. Patient characteristics are shown in Table 1. The median age of patients was 23 years (range 1 to 58 years). Twenty-eight patients were aged <10 years. One hundred thirty patients (85%) had hematologic malignancies. VZV titers were positive before ABMT in 139 patients and negative in 11 patients. VZV titers were not available for three patients. The median follow-up time of patients was 362 days.

VZV infection. Forty-three patients (28%) developed VZV infections after ABMT. One patient had two episodes of herpes zoster. The median onset of VZV infection was the fifth month after transplant (range 1 to 24 months) with 60% and 91% of cases occurring in the first 6 and 12 months after transplant, respectively. The actuarial incidence of VZV infection was 25% at 1 year (Figure 1). Pretransplant serologies were positive in 42 patients (98%) who developed VZV infection, indicating reactivation of latent virus. One patient who developed VZV infection had a negative VZV titer, which most likely represented a primary infection.

The onset of VZV infection occurred during complete remission in 32 patients, two of whom were in remission after chemotherapy for relapse after ABMT. Seven patients had relapsed when they developed VZV infection and were receiving chemotherapy. Four patients developed VZV infection while in remission but relapsed within 4 weeks of VZV infection. Seventy-nine percent of patients were treated with IV acyclovir, two patients received topical acyclovir, and two patients were treated with oral acyclovir. Four patients received no therapy.

Distribution of lesions. Thirty-three patients (77%) presented with localized herpes zoster. The dermatomes initially involved are shown in Table 2. There was no influence of underlying disease or previous radiation therapy on specific dermatomal presentation. Two types of disseminated zoster were observed, localized zoster with subsequent dissemination and varicella, both of which represent secondary infections due to reactivation of virus. Cutaneous dissemination developed in seven patients with localized herpes zoster; in one of the seven, cutaneous and probable visceral dissemination developed (this patient had interstitial infiltrates on chest roentgenogram and elevated liver function tests). Ten patients presented with varicella. Probable visceral dissemination developed in one of these patients who had elevated liver function tests concurrent with VZV infection. In one patient, a 9-year-old boy whose pretransplant VZV serology was negative and who had known exposure to VZV, the varicella infection probably represented a primary infection. The remaining nine patients all had serologic evidence of previous VZV infection and no known exposure to the virus antecedent to presentation after BMT. There were no statistically significant differences between patients who presented with varicella or localized herpes zoster in terms of underlying disease, sex, age, or preparative regimen (Table 1), although the numbers of patients are small and differences may have been missed.
cutaneous and visceral dissemination. Occurred in 21 (46%) patients with varicella, as localized herpes zoster, disseminated herpes zoster, or as varicella, which is also known as atypical generalized zoster.

In the present series, the overall frequency of VZV infection was 28%, which is comparable to that of earlier reports of VZV infections in selected immunocompromised patients. Most VZV infections occurred during the first 6 months after transplant, which is also the period of maximal immune dysfunction. VZV infection rarely developed after 1 year, which correlates with restoration of immune function and subsequent decline in reactivation of virus. The majority of patients (75%) presented with localized herpes zoster, with the thoracic and cranial dermatomes most frequently involved. Cutaneous dissemination developed in 21% of patients, and probable visceral dissemination developed in 5% of patients. Morbidity was not related to the initial presentation (localized v varicella) or to development of dissemination. There were no deaths as a result of VZV infection.

VZV infection after autologous BMT largely parallels that reported for allogeneic BMT recipients. The incidence, median time of onset, and morbidity appear to be similar in these two groups. Ljungman et al reported that 36% of allogeneic BMT patients developed VZV infections after BMT. The Seattle group reported that VZV infection occurred in 17% of leukemia and aplastic anemia patients who underwent autologous or syngeneic BMT. Twenty-four percent of these patients who survived >90 days free of VZV developed VZV infection, with a median time of onset of infection at 5 months.

In contrast, the risk factors associated with developing VZV infection are distinct for autologous and allogeneic BMT patients. Previous reports determined that the presence of GVHD was a strong predictor for VZV infections in allogeneic recipients. In the present series, underlying disease was the only risk factor associated with VZV infection. VZV infection occurred most frequently in patients with Hodgkin’s and non-Hodgkin’s lymphoma (46%) but in only 23% and 9% of patients with acute leukemia and solid tumors, respectively.

A similar relationship between risk of secondary VZV infection and underlying malignancy has been previously observed in patients who receive standard chemotherapy or radiation therapy. Patients with lymphoreticular malignancies have a much higher incidence of secondary VZV infection (15% to 35%, highest in patients with Hodgkin’s disease) as compared with patients with acute leukemia and solid tumors (2%). Therefore, other immunologic or nonimmunologic factors not associated with autologous BMT, but with the underlying disease or its treatment, may predispose to development of VZV infection. However, the overall risk of developing secondary VZV infection appears to be greater for each malignancy after ABMT as compared with the

### Table 2. Dermatomal Distribution of VZV Infection

<table>
<thead>
<tr>
<th>Presentation</th>
<th>No. of Patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Varicella</td>
<td>10/43 (23)</td>
</tr>
<tr>
<td>Visceral dissemination</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td>Dermatomal</td>
<td>33/43 (77)</td>
</tr>
<tr>
<td>Cranial</td>
<td>11/33 (33)</td>
</tr>
<tr>
<td>Cervical</td>
<td>2/33 (6)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>11/33 (33)</td>
</tr>
<tr>
<td>Lumbar</td>
<td>2/33 (6)</td>
</tr>
<tr>
<td>Sacral</td>
<td>7/33 (21)</td>
</tr>
<tr>
<td>Dissemination</td>
<td>7/33 (21)</td>
</tr>
</tbody>
</table>

*Six patients with cutaneous dissemination, and one patient with cutaneous and visceral dissemination.

### Table 3. Frequency of VZV Infection in Patients Grouped by Underlying Disease

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>No. with VZV/No. at Risk (%)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>20/88 (23)</td>
<td>.173</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>21/46 (46)</td>
<td>.002</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>2/25 (9)</td>
<td>.025</td>
</tr>
</tbody>
</table>

*P-values are comparisons of the proportion of patients with VZV infection in each underlying disease category as compared with the proportion of infected patients of all patients with all other underlying diseases.
same malignancy in patients receiving non-marrow-ablative therapy.

The rate of dissemination (45%) and mortality (10%) of VZV infection after allogeneic BMT in previous reports were higher than in the present series after ABMT.4 This may be related to greater depression of immune function in allogeneic patients, especially in the presence of acute and chronic graft-versus-host disease (GVHD).10,15 However, because few patients were analyzed and many of the patients included in the allogeneic series had VZV infections prior to the availability of acyclovir (which reduces the rate of dissemination and mortality from VZV infections in immunocompromised patients),16,17 this comparison is difficult to make. Most patients in the present series were treated with acyclovir, which probably affected their outcome.

Clinical infection with VZV is dependent on reactivation of latent virus and subsequent development of infection with typical cutaneous lesions.18 The degree of host immunocompetence most likely influences the latter. Factors responsible for viral reactivation on a molecular basis are unknown. Ljungman et al reported that 26% of allogeneic recipients had subclinical evidence for reactivation of VZV, suggesting that 62% of their patients had VZV reactivation (clinical plus subclinical).4 It would be interesting to know whether the greater frequency of VZV infection in patients with lymphoma in this series is due to a higher rate of viral reactivation or whether it is due to a greater likelihood of clinical expression of viral reactivation.

In this series, VZV infection developed in 28% of patients undergoing ABMT, a percentage similar to that reported for allogeneic BMT recipients and other immunosuppressed patients. Patients with Hodgkin's and non-Hodgkin's lymphoma were identified as a particularly high-risk group; nearly 50% of these patients developed VZV infection. This could be an appropriate group to target for evaluation of prophylactic antiviral drugs such as acyclovir or other agents with significant anti-VZV activity. Because ABMT is being used increasingly to treat patients with a variety of malignancies, patients and physicians should be advised of this common late post-BMT infection so that patients receive prompt antiviral therapy that significantly reduces mortality and that may reduce the morbidity associated with VZV infection.

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