Herpes Zoster Infection After Autologous Bone Marrow Transplantation

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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.

AUTOLOGOUS 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\(^{1,2}\).

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.\(^4\) 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.\(^3\) Patients received either busulfan (BU) plus cyclophosphamide (Cy) or Cy and total body irradiation (TBI). Marrow was purged by 4-hydroxycyclophosphamide before cryopreservation as described previously.\(^4\) No systemic chemotherapy or immunotherapy was administered post-transplant. General infectious disease management included empiric antibiotics in granulocytopenic patients with first fever. After 1981, prophylactic miconazole [5 mg/kg intravenously (IV) every 8 hours] was started with first fever, and acyclovir [250 mg/m\(^2\) IV every 8 hours in HSV-positive patients] was started four days before BMT.

Both medications were continued until resolution of granulocytopenia. All patients were in protective isolation during period of granulocytopenia. Trimethoprim-sulfamethoxazole was administered to patients with acute leukemia as CNS consolidation after recovery of counts, generally 2 or 3 months after BMT. Patients were discharged from the hospital at the time of resolution of granulocytopenia. After 50 days, if the patients were clinically stable, their clinical condition was followed by their referring physicians; patients returned 6 and 12 months after transplant for follow-up.

VZV serologic tests were performed using an immunofluorescence assay before transplant. Titers \( \geq 1:8 \) were considered positive.

Definitions. VZV infection was defined as the appearance of classical vesicular cutaneous skin lesions and/or identification of VZV virus by its typical cytopathologic effect on initial culture and after passage. Herpes zoster was defined as vesicular lesions beginning in a dermatomal distribution. Cutaneous dissemination of herpes zoster was defined as the subsequent development of six or more skin lesions that did not conform to any dermatome. 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 dermatomal distribution irrespective of previous VZV infection. Visceral dissemination of varicella was specified as above. Postherpetic neuralgia was defined as dermalomatous 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 using the Cox proportional hazards model. The relative risk was calculated as the ratio of the hazard rates of the two groups compared.
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. Differences 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.

![Graph showing Actuarial probability of VZV infection after ABMT](Image)
Outcome. Complications from VZV infection occurred in 32% of patients and included postherpetic neuralgia (five), scarring (six), alopecia (one), and neurologic dysfunction, (deltoid muscle weakness from localized thoracic herpes zoster in one patient and urinary retention from sacral herpes zoster in the other). Complications occurred equally in patients, regardless of presentation (herpes zoster or varicella) or subsequent dissemination. No patients developed encephalitis. Despite the high incidence of cranial involvement, there were no ophthalmic complications. Because of small numbers, it is not possible to correlate antiviral treatment with type or frequency of complication. No deaths were related to VZV infection.

Risk factors for VZV infection. With univariate and multivariate analysis, we evaluated a number of risk factors for their predictive value of a VZV infection. The only significant risk factor was underlying disease. VZV infection occurred in 21 (46%) patients with Hodgkin's or non-Hodgkin's lymphoma as compared with 20 (23%) with leukemia, and two (9%) with solid tumors (P < .002) (Table 3). Age, sex, preparative regimen, survival, positive or negative VZV titer, disease status, or previous radiation therapy were not predictors for development of VZV infection.

DISCUSSION

Infections in BMT recipients account for significant treatment-related morbidity and mortality. Most of these infections occur during neutropenia; however, despite resolution of neutropenia, these patients remain at great risk for infections as a result of profound and persistent abnormalities in immune function. Viral infections represent one of the most frequent causes of infection in the post-BMT period and are usually due to viruses in the herpes family, including HSV, cytomegalovirus (CMV), and VZV. These are generally secondary infections which are due to reactivation of latent virus rather than new, primary infections.

The incidence of VZV infection in seropositive cancer patients or patients receiving immunosuppressive therapy is between 5% and 52%. This reactivation of virus can present 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 or 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 the 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 allogeneic 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

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### Table 2. Dermatomal Distribution of VZV Infection

<table>
<thead>
<tr>
<th>Presentation</th>
<th>No. of Patients (%)</th>
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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>
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<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>
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*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. 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). 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), 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. 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). 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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REFERENCES

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