Recent Steroid Therapy Increases Severity of Varicella Infections in Children With Acute Lymphoblastic Leukemia

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ABSTRACT. Objective. The varicella-zoster virus (VZV) continues to be a dangerous pathogen to immunocompromised children. Children with acute lymphoblastic leukemia (ALL) are treated with intermittent steroid therapy. This study was undertaken to examine the relationship between steroid therapy for ALL and severity of varicella infection.

Methods. We performed a retrospective review of patients who were on Pediatric Oncology Group Protocol 9201 and had a history of varicella infection. Pediatric Oncology Group 9201 is a phase III study for the treatment of children with lesser risk ALL diagnosed between 1992 and 1999. Cases of varicella were coded 1 to 5 on the basis of severity: grade 1 caused minimal to no symptoms, grade 2 caused mild to moderate symptoms that did not require hospitalization, grade 3 caused symptoms severe enough to require hospitalization and intravenous acyclovir, grade 4 caused severe disease that had complications or that required intensive care, and grade 5 resulted in death.

Results. Of 697 enrolled patients, 110 (15.8%) developed primary varicella; 59% of these were male. For analysis, disease grade was dichotomized into nonsevere (grades 1 and 2) and severe (grades 3, 4, and 5). Of the 110 patients, 56 had nonsevere disease; 54 had severe disease, including 2 deaths. Of the patients whose varicella was diagnosed within 3 weeks of receipt of prednisone, 70% had severe infection, whereas only 44% of those who had not received prednisone within 3 weeks had severe infection. The odds ratio for having a severe infection within 3 weeks of prednisone versus >3 weeks is 2.9 (95% confidence interval: 1.1–7.9). By multivariate analysis, older age at ALL diagnosis, years from ALL diagnosis to VZV diagnosis, and VZV diagnosis within the 4-week period of interest (during or within 3 weeks of prednisone therapy) all were independently associated with an increased risk for severe infection.

Conclusions. This study represents the largest study to date of varicella in children with ALL and provides convincing evidence that prednisone therapy during the VZV incubation period significantly increases the risk for developing severe varicella infection. In addition, older age is associated with more severe infection. Despite the varicella vaccine and a dropping incidence of primary infections, VZV remains a dangerous pathogen for pediatric patients with ALL. With the possible exception of induction therapy, patients who are on ALL therapy and are exposed to varicella should have steroid therapy delayed until after the VZV incubation period. These findings may have implications for other diseases that are treated with corticosteroids. Pediatrics 2005;116:e525–e529. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0219; varicella, prednisone, steroids, leukemia, children.

ABBREVIATIONS. VZV, varicella-zoster virus; ALL, acute lymphoblastic leukemia; POG, Pediatric Oncology Group; VZIG, varicella-zoster immune globulin; OR, odds ratio; CI, confidence interval.

The varicella-zoster virus (VZV) is well recognized as a potential cause of morbidity and mortality in immunocompromised children. Small series and case reports in children have noted an association between steroid therapy and severe VZV infections.1–8 In children with acute lymphoblastic leukemia (ALL), steroid therapy and its relation to VZV severity have not been well studied. We hypothesized that patients who received recent (within 3 weeks) steroid therapy for ALL were at higher risk for severe varicella infection compared with those who had not been treated recently (>3 weeks) with steroids.

METHODS

With approval from our Institutional Review Board and the ALL Committee Chair of the Pediatric Oncology Group (POG), we performed a retrospective review of patients who were on POG Protocol 9201 and had a history of varicella infection. Data were abstracted from patient-specific protocol flow sheets regarding demographics; blood counts; VZV titers; date of ALL diagnosis; and clinical aspects of the patients’ varicella infections, including date of varicella diagnosis, dates of most recent prednisone therapy, severity of infection, VZV immune globulin (VZIG) administration, acyclovir administration, weight at the time of VZV infection, and outcome. Data were unavailable regarding timing of VZIG administration relative to exposure, VZIG dosing, acyclovir dosing, and vaccination rates at the time of ALL diagnosis in this population.

POG 9201 is a phase III study for the treatment of children who were aged 1 to 10 years and had lesser risk ALL diagnosed between 1992 and 1999. In addition to other chemotherapy agents, POG 9201 included a 4-week induction with prednisone at a dose of 40 mg/m2 per day (maximum 60 mg/day) orally divided 3 times a day for 28 days, followed by 1-week pulses of prednisone (same dose) at weeks 8, 17, and 25, then every 16 weeks until week 105. Vincristine (1.5 mg/m2 per dose; maximum 2 mg/dose) was given on days 1 and 8 of each prednisone pulse.

Cases of varicella were coded 1 to 5 on the basis of severity:
grade 1 caused minimal to no symptoms, grade 2 caused mild to moderate symptoms that did not require hospitalization, grade 3 caused symptoms severe enough to require hospitalization and/or intravenous acyclovir, grade 4 caused severe disease that had complications or that required intensive care, and grade 5 resulted in death. For the purposes of analysis, we dichotomized disease grade into nonsevere (grades 1 and 2) and severe (grades 3, 4, and 5). Patients were classified as underweight when their weight at the time of VZV diagnosis was ≥5th percentile, as normal weight at 6th to 94th percentiles, and as overweight at ≥95th percentile. A child’s VZV was diagnosed in the 4-week period of interest when it was diagnosed during the week of or within 3 weeks of completion of prednisone therapy. A 2 × 2 table was analyzed with the Pearson χ² test. For investigating the effect of being diagnosed in the 4-week period of interest accounting for other factors, a full logistic model was fit. The full model included 7 variables: age at ALL diagnosis, years from ALL diagnosis to VZV diagnosis, race/ethnicity, gender, VZIG use, weight class, and VZV diagnosis in the 4-week period of interest. Acyclovir use was not included because virtually all of the patients (with known acyclovir use status) were in fact given acyclovir. A full model fit in which all variables are included and none is dropped results in a more accurate Value for the variable of interest. The odds ratio (OR) for age at ALL diagnosis represents the OR for each additional year of age. That is, the OR for a 5-year-old compared with a 4-year-old is 1.4, whereas the OR for a 6-year-old compared with a 4-year-old is 1.4 × 1.4 = 2.0. Similarly, the OR for years from ALL diagnosis represents the OR for each additional year from ALL diagnosis to VZV diagnosis.

RESULTS

Of 697 enrolled patients, 110 (15.8%) patients had 114 diagnoses of varicella made. Four patients had 2 varicella infections, and these 4 secondary cases were excluded from analysis. Table 1 shows demographic and clinical data. Of the 110 patients with primary varicella, 65 (59%) were male. No patients were reported as having grade 1 disease; 56 patients had grade 2 disease, 48 had grade 3 disease, 4 had grade 4 disease, and 2 had grade 5 disease (resulting in death). The patients with severe cases were on average older at time of ALL diagnosis (P = .03) and at time of VZV diagnosis (P = .002) than patients with nonsevere cases. The severe cases also had a longer mean interval from ALL diagnosis to VZV diagnosis (P = .02). The median time from ALL diagnosis to varicella diagnosis was 65.4 weeks (range: 9.4–125.3 weeks). No cases of varicella were diagnosed during the 28-day remission induction period of ALL therapy or the 3 weeks after induction. Eight (7%) patients were classified as underweight, 90 (82%) as normal weight, and 12 (11%) as overweight. Compared with normal weight, underweight was associated with severe infection and overweight with nonsevere infection by univariate analysis (P = .02). Comparing nonsevere with severe cases, there were no significant differences in race/ethnicity, gender, absolute neutrophil count at VZV diagnosis, VZIG administration, acyclovir administration, or VZV titer at ALL diagnosis (Table 1).

The median number of days from prednisone treatment to varicella diagnosis was 49 for nonsevere (grade 2) varicella, 42 for grade 3, 21 for grade 4, and 5 for grade 5. Table 2 presents the numbers and percentages of severe and nonsevere cases that were diagnosed in and outside the 4-week period of interest (composed of the week of prednisone therapy and the following 3 weeks). Of the patients whose varicella was diagnosed within 3 weeks of receipt of prednisone, 16 (69.6%) of 23 had severe infection, whereas only 38 (43.7%) of 87 of those who had not received prednisone within 3 weeks had severe in-

| Table 1. Demographic and Clinical Data of Patients With ALL and Varicella Infection |
|----------------------------------|------------------|------------------|------------------|------------------|
| Nonsevere Cases                  | Severe Cases     | Overall          | P Value          |
| (N = 56)                         | (N = 54)         | (N = 110)        |                  |
| Age at ALL diagnosis, y (mean SE)| 3.8 (0.2)        | 4.5 (0.3)        | 4.1 (0.2)        | .03              |
| Age at VZV diagnosis, y (mean SE)| 4.9 (0.2)        | 5.9 (0.2)        | 5.4 (0.2)        | .002             |
| Years from ALL to VZV, mean (SE)| 1.1 (0.1)        | 1.4 (0.1)        | 1.3 (0.1)        | .02              |
| ANC at VZV diagnosis, mean (SE)  | 2049 (280)       | 2002 (232)       | 2022 (178)       | .9               |
| Weight class, %                  |                  |                  |                  |                  |
| Underweight (<5th %ile)          | 2                | 13               | 7                | .02              |
| Normal (6th–94th %ile)           | 82               | 81               | 82               |                  |
| Overweight (>95th %ile)          | 16               | 6                | 11               |                  |
| Race/ethnicity, %                |                  |                  | .1               |                  |
| White non-Hispanic               | 77               | 57               | 67               |                  |
| Hispanic                         | 13               | 28               | 20               |                  |
| Black                            | 5                | 4                | 5                |                  |
| Other                            | 5                | 11               | 8                |                  |
| % Male                           | 63               | 56               | 59               | .5               |
| VZIG, % yes                      | 36               | 30               | 33               | .5               |
| Acyclovir, %                     |                  |                  | .5               |                  |
| Yes                              | 84               | 96               | 90               |                  |
| No                               | 2                | 0                | 1                |                  |
| Unknown                          | 14               | 4                | 9                | .9               |
| VZV Titer, %                     |                  |                  |                  |                  |
| Positive                         | 18               | 20               | 19               |                  |
| Negative                         | 38               | 46               | 42               |                  |
| Unknown                          | 45               | 33               | 39               |                  |
| Disease grade, n (%)             |                  |                  |                  |                  |
| 1                                | 0                | 0                |                  |                  |
| 2                                | 56 (100)         | 56 (51)          |                  |                  |
| 3                                | 49 (89)          | 49 (44)          |                  |                  |
| 4                                | 4 (7)            | 4 (4)            |                  |                  |
| 5                                | 2 (4)            | 2 (2)            |                  |                  |

ANC indicates absolute neutrophil count.
In addition, a trend was noted toward underweight status being associated with severe infection and overweight with nonsevere infection ($P = .06$; Table 3). When varicella was diagnosed within the 4-week period of interest, the multivariable logistic model estimated OR of having a severe case was 5.0 (95% confidence interval [CI]: 1.5–17.0; $P = .01$) compared with varicella's being diagnosed outside the 4-week period of interest. Race/ethnicity, gender, and absence of VZIG administration were not associated with severe infection.

Both deaths occurred in children who had been treated recently with prednisone. The first involved a 6-year-old Hispanic boy who was admitted with back pain 3 days after completing week 73 of prednisone therapy. The pain generalized, and he developed a vesicular rash on his inner thighs and genitalia that were culture positive for varicella. Acyclovir was started at the onset of the rash, but he quickly progressed to multiorgan failure and died on hospital day 15.

### DISCUSSION

The VZV vaccine was approved by the US Food and Drug Administration in 1995.9 Despite its widespread use during the period of this study and a dropping incidence of primary infections in the general population, VZV remains a dangerous pathogen for immunocompromised patients, including children with ALL.9–13 This study represents the largest study to date of varicella in children with ALL and provides convincing evidence that prednisone therapy during the VZV incubation period (10–21 days) significantly increases the risk for developing severe varicella infection. These results suggest that if a child who is on therapy for ALL has a documented varicella exposure, then prednisone therapy should be deferred until after the incubation period, even if the patient was previously vaccinated and/or treated with VZIG. The exception to this approach may be the child who is exposed to varicella just before or during ALL remission induction therapy, during which the child typically is given 28 consecutive days of steroid therapy. This situation presents a challenging decision. This did not occur in our patients, and no data exist in the literature as to the best approach. The obvious risks of induction failure versus disseminated VZV must be weighed, and each patient should be treated on an individual basis depending on the nature of the exposure and clinical status. Thus, induction therapy for ALL may be a time when steroid therapy should not be altered.

In addition to possibly withholding steroid therapy, the empiric use of oral acyclovir may be considered after a child with ALL is exposed to VZV, although its efficacy has not been established in this...
setting. Exposed patients should also be treated with VZIG as soon as possible after exposure, although it should be noted that VZIG may extend the incubation period of VZV up to 28 days. Although few data exist, it is probably safe to continue immunotherapy (6-mercaptopurine, methotrexate) and vincristine during the VZV incubation period. It should be noted, however, that varicella has been fatal in at least 1 child who had ALL and was receiving methotrexate only, albeit in the pre-VZIG/acyclovir era.

An association between steroid use and severe varicella has been recognized for decades, although most reports have come from relatively small retrospective series and case reports. Furthermore, methodologic flaws and the paucity of data regarding types, doses, and routes of administration of corticosteroids have hampered the certainty of this association, particularly for children with asthma and other nonmalignant diseases. Oral steroids also have been shown to decrease the efficacy of the VZV vaccine.

Both of the patients who died in this report presented with back pain as an initial symptom. This is consistent with previous reports (totaling 31 patients who died after similar presentations) that abdominal and/or back pain, often preceding the appearance of skin lesions, is an ominous sign and portends a severe course. Thus, in an immunocompromised patient with unexplained back or abdominal pain, the early empiric use of acyclovir should be considered, even in the absence of other symptoms or signs of varicella. Both patients in this report first developed vesicles in the genital area, highlighting the need for a thorough skin examination in the febrile immunocompromised patient. These cases also illustrate that the previous administration of the varicella vaccine and the appropriate use of VZIG and acyclovir are not always protective against severe varicella infection.

We also noted an association with older age and more severe disease, an association previously reported. The reason in our series for the association of severe cases with a longer lag time from ALL diagnosis to VZV diagnosis is unknown, although it may be related to the patients’ nutritional status, which may deteriorate with ongoing chemotherapy. We found that being overweight is a risk factor for severe varicella infection in this population, whereas being overweight had a protective effect. Independent of timing of infection, this association likely reflects underweight children’s poor nutritional status as a component of their ability to fight infection. It should be noted, however, that weight alone is not an independently accurate marker for nutritional status. A recently published report found that both overweight and underweight children with acute myelogenous leukemia have significantly higher treatment-related mortality, mostly from infection.

We did not find race/ethnicity to be associated with severe infection. However, there was a trend toward more severe disease in Hispanic patients, who composed 20% of the study population, compared with white non-Hispanic patients (estimated OR: 2.8; 95% CI: 0.9–8.7). Black patients composed only 5% of the study population. It is possible, therefore, that true ethnic risk factors may exist, but the limited numbers of patients in this study do not allow statistical conclusions from these data.

In addition to having therapeutic implications, this study provides evidence that children with ALL should be immunized against VZV (because 16% of patients in this series developed varicella and half of those had at least grade 3 disease). The vaccine is safe and effective for selected children with ALL in remission, and it is also cost-effective. Many clinicians, however, are reluctant to administer the vaccine to children who are on therapy for ALL, and at least 1 current ALL study within the Children’s Oncology Group recommends not administering the vaccine. This issue deserves larger prospective studies. It has been recommended that steroid therapy be withheld 1 week before and 2 weeks after VZV vaccination to decrease the risk for vaccine-associated rashes and that all chemotherapy be held 1 week before and after vaccine administration. Among household contacts, the VZV vaccine is highly effective at preventing moderate and severe disease, and it should be given to siblings of immunocompromised children.

The rates of varicella in the United States have dropped since the implementation of the vaccine. This should lead to decreased rates of exposure and disease in children with leukemia, but this has not yet been documented. Because of the dropping incidence of varicella, prospective studies to assess the relationship between steroids and varicella are unlikely. A clinical situation arising more frequently at present is that of a previously immunized child who has a diagnosis of ALL. It is recommended that VZV titers be ascertained at diagnosis, but even when positive, these patients are usually treated as antibody negative because of their immunocompromised state during chemotherapy.

We did not find a correlation between the use of VZIG and acyclovir in preventing severe disease; however, data regarding the doses and timing (relative to exposure) of VZIG administration and start dates and doses of acyclovir administration were unavailable for many patients. Because the efficacy of VZIG and acyclovir depend on early initiation and appropriate dosing, these findings must be interpreted with caution. Specifically, in accordance with the Committee on Infectious Diseases of the American Academy of Pediatrics, we strongly recommend VZIG and acyclovir administration in the appropriate settings.

This study is limited by its retrospective nature and inclusion of only lesser risk ALL patients. It is likely, however, that children with standard and high-risk ALL would be equally (if not more) jeopardized by steroid therapy during the varicella incubation period because they are treated with more intensive chemotherapy regimens. This study addressed only primary varicella infections and not zoster infections. For the majority of cases of varicella in this report, the diagnosis was made clinically and not confirmed by laboratory testing. In this study, no
patients were reported as having grade 1 disease. This is not unexpected given that all of the patients on POG 9201 were immunocompromised and thus were likely to have relatively more severe disease (compared with immunocompetent children). It is possible that grade 1 varicella occurred in this population but never came to medical attention. Finally, this study did not assess the risk of dexamethasone for varicella severity. Several studies have suggested that dexamethasone is more toxic than prednisone in the treatment of ALL, but it is not known whether their immunosuppressive properties are comparable. It is likely, however, that dexamethasone (at comparable doses) is at least as immunosuppressive as prednisone.

In conclusion, varicella remains a dangerous pathogen for pediatric patients with ALL. Pediatric patients who have lesser risk ALL and receive prednisone within 3 weeks before varicella diagnosis are at higher risk for severe infection compared with those who had not received steroid therapy within 3 weeks. With the possible exception of induction therapy, patients who are on therapy for ALL and are exposed to varicella should have steroid therapy delayed until after the VZV incubation period. This may have implications for other diseases that are treated with corticosteroids.

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