Incidence and consequences of varicella in children treated for cancer in Guatemala

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Background: **Varicella-zoster virus infection is associated with significant morbidity and mortality in immune-compromised children, despite treatment with antiviral agents. Universal varicella vaccine programs have significantly decreased this risk in many high-income countries, but in most low-income and middle-income countries, the burden of varicella in children treated for malignancy is poorly defined.**

Methods: **We retrospectively reviewed records of children at the National Unit of Pediatric Oncology (UNOP) in Guatemala diagnosed with varicella between January 2009 and March 2013 in order to calculate incidence of varicella and evaluate morbidity, mortality, treatment interruption, and cost.**

Results: **Fifty-nine cases of varicella were identified. Incidence was 23.4 cases per 1000 person-years (p-y). 66.1% of cases occurred in children with leukemia (median age 5.2 years; interquantile range 3.4-7 years) and 41.0% of these occurred during maintenance therapy. Source of exposure was identified for 14/59 (23.7%) children. Most were hospitalized (71.2%) and given intravenous acyclovir (64.4%). Eight (13.6%) children required critical care, and two (3.4%) died from disseminated varicella with multi-organ failure. Chemotherapy was delayed or omitted due to varicella in 50%. No significant differences in outcomes based on nutritional and immunologic status were detected. The minimum average cost of treatment per episode was 598.75 USD.**

Conclusions: **Varicella is a significant problem in children treated for cancer in Guatemala, where effective post-exposure prophylaxis is limited. In the absence of universal varicella vaccination, strategies to improve recognition of exposure and the future use of novel inactivated vaccines currently under investigation in clinical trials could mitigate this burden.**

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Introduction

Children in low- and middle-income countries (LMIC) are increasingly diagnosed and treated for cancer.[1] Compared with children in high-income countries (HIC), children in LMIC are disproportionately affected by treatment-related mortality (TRM), defined as death due to adverse effects of treatment rather than disease progression.[2-8] In children with acute lymphoblastic leukemia (ALL), TRM has been estimated to be in the range of 11-21% in LMIC, compared with 1-3% in HIC.[2-7] As the largest contributor to TRM, infectious complications such as varicella have a greater impact on outcomes and costs of pediatric cancer in LMIC.[2-7]

Varicella-zoster virus (VZV) infection causes significant morbidity and mortality in immune-compromised children, including those undergoing treatment for cancer.[9-11] Previous studies have reported the risk of disseminated infection in these patients, in the absence of prophylaxis or treatment with acyclovir, to be approximately 32%-50%.[12] Inclusion of the live-attenuated varicella vaccine in the routine childhood

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immunization schedule has dramatically reduced rates of varicella in both immune-competent and immune-compromised children in many HIC.[13-15] In most LMIC, however, the high cost and lower priority of this vaccine compared with other life-saving vaccines has discouraged its inclusion in universal vaccination programs.[16]

The current study sought to determine the burden and consequences of varicella in children who had been treated for cancer in Guatemala City and to provide a preliminary assessment of associated costs, in order to inform public policy with regard to potential prophylaxis strategies.

Methods

A retrospective analysis of medical records from children treated for cancer who were diagnosed clinically with primary varicella was conducted between January 2009 and March 2013 at the National Unit of Pediatric Oncology (UNOP) in Guatemala City, Guatemala. UNOP is a 48-bed facility specializing in the treatment of cancer in children and adolescents, staffed by 35 physicians, including six pediatric oncologists and 104 nurses. UNOP is the most advanced center for treatment of pediatric cancer in Guatemala, a lower-middle-income country of approximately 14 million people and sees approximately 400 new cases and 2000 inpatient admissions annually. All cancers are treated; hematopoietic stem cell transplantation is not offered. Approximately 30% of patients have advanced disease at diagnosis and 50% of those newly diagnosed with ALL are undernourished, although nutritional status improves with support during cancer therapy.[17,18]

Standard practice at UNOP at the time of the study was to treat varicella only when children presented to the clinic with symptoms; varicella-zoster immune globulin for post-exposure prophylaxis is unavailable and acyclovir was not used for this purpose. Laboratory-based diagnostic tests are not used, nor do patients undergo serologic screening. Once symptomatic, patients are typically admitted for intravenous (IV) acyclovir. Factors considered in deciding to admit a patient include the availability of inpatient beds, severity and duration of illness prior to presentation, and immune status (i.e. patients off-therapy at the time of infection were less likely to be admitted).

There were no exclusion criteria based on age or malignancy. Off-therapy patients who continued to receive care at UNOP were not excluded. Participants were identified through three sources: 1) paper surveillance records completed for any episode of varicella (2009-present); 2) the UNOP Pediatric Oncology Networked Database (POND4Kids), supported by St. Jude Children's Research Hospital, which includes all patients at UNOP and identifies those with varicella (2009-present); and 3) UNOP's electronic database of infectious complications in admitted patients (2011-present).[19] Between July 2010 and May 2011, no cases were identified from any source; this was presumed due to a transition in infection control staffing and associated failure of reporting rather than true absence of varicella; therefore, this period was excluded from the denominator used to determine incidence.

Data for each participant was extracted from POND4Kids® (St. Jude Research Hospital, TN, USA) and entered into a REDCap database® (2014 Vanderbilt University, TN, USA).[20] Original medical records were reviewed to obtain missing data. Data were collected regarding the patient's past medical history (primary malignancy, date of diagnosis, treatment protocol, cycle at the time of varicella, history of prior serious infections) and varicella diagnosis (date, exposures, symptoms, results of laboratory tests and imaging), treatment (clinic visits, hospitalization, dosing and duration of antiviral drugs), and outcomes. Primary outcomes were morbidity, defined as any complication attributed to varicella, including pneumonia, hepatitis, meningoencephalitis, or secondary bacterial infections; mortality, defined as death from varicella or its complications (death from progression of malignant disease or other causes after recovery from varicella was not included); and treatment interruption, defined as any delay or omission of scheduled chemotherapy, surgery or radiation.

Determination of minimum costs

Costs were obtained from UNOP administrative electronic records. Median days of hospitalization, mean days of IV acyclovir at a standard dose of 1500 mg/m^2, and median body surface area were used in order to calculate the minimum average expenses per episode of varicella. Additional costs of complications, including ICU beds and ICU-related procedures, were not included in this calculation. Outpatient therapy was not documented in medical records; mean duration of oral acyclovir was estimated based on local standard of care (administration of acyclovir intravenously until all lesions crusted, followed by oral acyclovir for a minimum of seven days total therapy).

Statistical methods

To calculate incidence of varicella among pediatric cancer patients, we defined the time at risk from the later of the initiation of the study (for patients diagnosed with cancer prior to January 1, 2009) or the date of diagnosis of

malignancy (for patients diagnosed with cancer after January 1, 2009) until the earlier of the conclusion of the study (March 31, 2013), date of diagnosis of varicella, or last follow-up date, excluding the period of missing data (July 1, 2010 to May 31, 2011). The numerator was the number of varicella cases during this period. The denominator (total person-years [p-y] at risk) was the sum for all patients of the time at risk.

Descriptive statistics were calculated for each variable. Categorical variables were presented with number of responses and percent of total for each category. Numeric variables were analyzed by number of responses, means, medians and interquartile ranges (IQR). Each outcome was compared by nutritional status, therapy status (on- or off-therapy), presence of neutropenia [neutropenia was defined as an absolute neutrophil count (ANC) less than 500 neutrophils/mm^3] and absolute lymphocyte count (ALC) at diagnosis of varicella. SAS macros provided by the World Health Organization (WHO) were used with SAS version 9.3 to calculate the weight-for-height and body mass index Z-scores.[21] Patients with *Z*-scores of less than -3 were classified as severely malnourished. Chi-square tests were used to assess differences in morbidity, mortality, complications and treatment interruption between groups. When the assumptions of the Chi-square test were not met, Fisher's exact tests were used. The analyses were performed using R version 2.15.3.[22] *P* values less than 0.05 were considered significant.

Results

Between January 2009 and March 2013, excluding July 2010 through May 2011, 59 children treated for cancer were diagnosed with varicella. Patient characteristics are shown in Table 1. There was a male predominance, in agreement with the larger population at UNOP, which was approximately 60% male. The median age for patients with varicella was 5.2 years (IQR: 3.4-7). Among 39 patients with leukemia, 16 (41.0%) were receiving maintenance, eight (20.5%) were in induction, nine (23.1%) were in consolidation, and six (15.4%) were off-therapy.

Table 1. Characteristics of patients diagnosed with varicella

Varables	Patients (*n*=59)
Age (y)	
Median (IQR)	5.2 (3.4-7)
Mean (range)	7.1 (1-14)
Sex, *n* (%)	
Female	17 (28.8)
Male	42 (71.2)
Type of malignancy, *n* (%)	
Leukemia	39 (66.1)
Lymphoma	10 (16.9)
Solid tumor	10 (16.9)
Identifiable exposure, *n* (%)	
Yes	14 (23.7)
No	45 (76.3)
Therapy status, *n* (%)	
Receiving chemotherapy	46 (78.0)
Receiving radiation only	3 (5.1)
Off therapy	10 (16.9)

IQR: interquartile range.

Incidence of varicella

During the observation period, 1394 children were newly diagnosed with cancer; and 1043 children diagnosed prior to 2009 were actively followed at UNOP during this period. The denominator was 2523 person-years and the median period of observation was 0.94 person-years (IQR: 0.14-1.74). The overall incidence of varicella in this population was estimated at 23.4 cases per 1000 p-y. Most families (76.3%) could not identify a source of exposure. Of the 14 cases with a known source, nine (64.3%) involved household contacts, and three (21.4%) were exposures within UNOP that were not temporally associated. The mean time elapsed between exposure and diagnosis of varicella was 12.7±5.3 days. Six (10.2%) children were diagnosed with varicella while admitted for other therapy; however, none identified a source of exposure in or outside the hospital.

Management

Patients had a median of one outpatient clinic visits per episode of varicella (IQR: 0-2), including both diagnostic and follow-up visits. Forty-two (71.2%) children with varicella were hospitalized for a median of six days (IQR: 1-11); and 36 (61.0% of all children; 85.7% of those hospitalized) received IV acyclovir for a median of six days (IQR 2-10). Since duration and dosing of oral acyclovir after discharge was not documented, we generated estimates based on the standard of care: When the duration of IV acyclovir was less than seven days, patients were discharged on oral acyclovir to complete a total of seven days of therapy (IV plus oral). Seventeen of 36 patients (47.4%) received less than seven days of IV therapy, with a median of four days in this group (IQR: 2.25-5.75), and therefore should have received oral acyclovir after discharge for a median of three days.

Forty-six patients (78%) were receiving chemotherapy when diagnosed with varicella; of these, 23 (50%) had a delay or omission of chemotherapy attributed to varicella or its complications. Median duration of treatment interruption was 10 days (IQR: 4-16; range: 4-25 days). Three of 5 children scheduled to undergo surgery or radiation had a delay in these procedures that was attributable to varicella.

Attributable morbidity and mortality

Twelve patients (20.3% of all patients and 26.1% of those receiving chemotherapy) experienced at least

one complication of varicella (Tables 2 and 3). Eight (13.6%) were admitted to the ICU. The median length of the stay in the ICU was 3 days (IQR: 2-4). The presence of any complication increased the median number of days hospitalized from 3 to 8 (P=0.03), compared with patients without complications. Three children were transferred to the ICU for respiratory distress and three were missing documentation regarding ICU transfer and care. Two children were transferred due to multi-organ failure from disseminated varicella and both subsequently died in the ICU, a case fatality rate of 3.4%.

Only therapy status (on-therapy) was a significant risk factor for morbidity (P=0.03). No statistically significant differences in hospitalization, morbidity, or mortality correlated with ANC, ALC, therapy status, or nutritional status. Fewer than 5% of participants were malnourished.

Costs

The cost of an inpatient bed per day at UNOP is approximately 88.58 U.S. dollars (USD). The cost of intravenous acyclovir is 13.91 USD per 250 mg; oral acyclovir is 13 cents per 400 mg tablet. The minimum average costs based on the median length of stay (6 days; 531.48 USD) and duration of IV acyclovir therapy (6 days at a median dose of 1200 mg/day; 66.77 USD), and estimated median duration of oral therapy based on standard of care (one day at a median dose of 1560 mg/day; 0.50 USD). Therefore, the estimated minimum average cost of an episode of varicella was 598.75 USD.

Table 2. Complications of varicella

Complications	Number of patients affected,* n (%)
No complications	47 (79.7)
Any complication	12 (20.3)
Varicella pneumonia/pneumonitis	4 (6.8)
Hepatitis (ALT/AST >3 upper limit of normal for age and not attributable to chemotherapy)	3 (5.1)
Unknown (ICU admission without documented indication for transfer)	3 (5.1)
Secondary soft tissue infections	2 (3.4)
Disseminated disease (multi-organ failure)	2 (3.4)
Neurologic complications (meningitis or encephalitis)	1 (1.7)
Secondary invasive bacterial infections (including pneumonia)	1 (1.7)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ICU: intensive care unit. *: Multiple complications were recorded in some patients.

Discussion

We confirmed that the incidence of varicella in children treated for cancer in Guatemala is significant and the disease is sometimes fatal. The incidence of 23.4 cases of varicella per 1000 p-y is lower than the rate of 46 cases per 1000 p-y reported in children with ALL in the U.S. prior to the adoption of routine vaccination. However, our lower estimate may be the consequence of our passive hospital-based surveillance and likely underestimates the incidence, as we did not exclude patients who had completed cancer therapy and no records exist for patients who may have suffered varicella but did not seek care.[11] These findings are also consistent with a previous retrospective study of 216

Table 3. Characteristics of patients who experienced complications of varicella

Subject	Age	Sex	Diagnosis	Complications	Therapy status	Nutritional status	Neutrophil count (cells/μL)
2	7	Female	Osteosarcoma in first remission	ICU admission: indication not documented	On chemotherapy	Moderately malnourished	Not documented
6	8	Male	Pre-B ALL, previous relapse	Death after 14 days secondary to disseminated varicella; ICU admission	On chemotherapy: consolidation	Adequately nourished	Not documented
17	3	Male	Pre-B ALL	Hepatitis	On chemotherapy: consolidation	Adequately nourished	1110
19	1	Male	Pre-B ALL	Hepatitis	On chemotherapy: induction	Adequately nourished	940
21	12	Male	T-cell ALL	Secondary soft tissue infection	On chemotherapy: induction	Moderately malnourished	630
22	6	Female	T-cell ALL	ICU admission: pneumonia	On chemotherapy: induction	Adequately nourished	840
35	6	Male	Pre-B ALL	ICU admission: VZV pneumonia	On chemotherapy: maintenance	Adequately nourished	2700
36	5	Male	Pre-B ALL	ICU admission: VZV pneumonia	On chemotherapy: maintenance	Overnourished	3370
38	2	Male	Pre-B ALL	ICU admission: indication not documented	On chemotherapy: induction	Adequately nourished	Not documented
52	7	Male	Hodgkin lymphoma	Death after 10 days secondary to disseminated varicella; ICU admission	On chemotherapy	Adequately nourished	4110
69	13	Male	Pre-B ALL	Secondary soft tissue infection	On chemotherapy: maintenance	Adequately nourished	3980
88	5	Male	Hodgkin lymphoma	ICU admission: indication not documented	On chemotherapy	Not documented	Not documented

ALL: acute lymphoblastic leukemia; ICU: intensive care unit; VZV: varicella-zoster virus.

Chilean children treated for malignancy between 1988 and 1997, which identified 79 children with varicella. While no varicella incidence data exist for healthy children in Guatemala, a meta-analysis from Latin America has shown that the incidence of varicella on children under 15 years is 42.9 cases per 1000 p-y (95% confidence interval: 26.9-58.9).[23] The mortality rate was 3.8%, with all deaths occurring during induction therapy for ALL despite early treatment with acyclovir. This mortality is over 100 times that of healthy children reported in Latin America[23] Leukemia was identified as a risk factor for severe infection, although we were not able to confirm this due to the small sample size of our study.[24]

Half of children who acquired varicella while receiving chemotherapy had their therapy delayed or omitted, which may influence long-term outcomes. It has been demonstrated that non-adherence to maintenance chemotherapy is a predictor of relapse in ALL; however, the consequences of treatment interruption for mild or moderate infection have not been established.[25] Our observed frequency of treatment interruption was comparable to the frequency in a study of children with ALL in maintenance therapy in the U.S. prior to vaccination, which reported chemotherapy delay or omission in 65% of those with varicella.[11]

The estimated cost to the healthcare system in Guatemala was a minimum of 598.75 USD per episode of varicella. This is an underestimate, since the cost of antibiotics and other non-antiviral medications, diagnostic procedures (especially in the ICU), and societal costs of a child's prolonged illness (such as absence from school or parental absence from work) were outside the scope of the current study. Moreover, while the cost of caring for patients in the ICU was not available to us, the aggregate sum for this would be much higher. This minimum estimate is nearly one-third the annual per capita income in Guatemala of 2740 USD, and a recent study categorized 73% of families at UNOP as below the poverty line.[17]

The universal use of varicella vaccine in young children has resulted in a 70%-98% decrease in the varicella incidence in the U.S. and other countries.[26-28] This policy provides varicella-specific immunity to most children prior to developing a malignancy and induces herd protection, decreasing the risk of transmission to those who lack adequate immunity due to their age, lack of response, or underlying disease. However, in many countries, including Guatemala, the risk of varicella morbidity for most children, does not clearly outweigh the costs of the universal vaccine program, in terms of both direct expenditure and resources diverted from other public health efforts.[16,29]

Limiting vaccination to immune-compromised patients is not feasible, since the current vaccine contains live-attenuated VZV, which may replicate unchecked and disseminate in severely immune-compromised children.[30,31] Vaccination of close contacts of immune-compromised children, such as varicella-susceptible siblings, could be a practical strategy. The benefit of administering the live varicella vaccine to potential contacts of immune-compromised patients far outweighs any theoretical risks of transmission.[32] In addition, since iatrogenic exposure in hospital and clinics is a problem in countries where varicella occurs with periodic epidemics, as observed in the current study, screening and immunizing susceptible health care workers in hospitals and clinics, as well as more rigorously screening of visitors could prevent some cases.[15] One effective solution may be available in the near future by two investigational non-live varicella vaccines, an inactivated whole VZV vaccine and a recombinant adjuvant VZV glycoprotein E vaccine.[33,34]

Alternatively, post-exposure prophylaxis has some potential to decrease morbidity and mortality of varicella in these children. Administration of VZV hyperimmune globulin (VZIG) can be effective, but is not available and is prohibitively expensive for most LMIC. Although post-exposure administration of acyclovir is recommended in some countries, and has recently been adopted in Guatemala, studies of prophylactic acyclovir have been questioned because of their limited sample size, lack of randomization, and inconsistent timing of initiation and duration of therapy.[32,35-38] The most recent review of practices found that approximately half of pediatric oncologists in the UK used acyclovir while half used VZIG, with no standardization of timing.[39,40] It is also unclear whether cell-mediated immunity is adequate to prevent rebound disease after cessation of acyclovir, and if acyclovir would interfere with the natural immune responses to varicella in immune-compromised patients.[41,42]

Post-exposure prophylaxis is mainly limited by the need to administer it within 10 days of exposure for VZV hyperimmune globulin and within a window of 7-10 days post-exposure for acyclovir.[10] Our report and others indicate that exposure to varicella is not recognized in 50-75% of patients who might benefit from this type of prophylaxis, despite established patient education.[11] This suggests the need for more intensive education for parents and other caregivers regarding signs and symptoms, as well for education targeting school settings and other locations where children are likely to be exposed. It also reflects barriers to identifying exposures in a densely populated urban environment where varicella is endemic.

Limitations of our study included: the retrospective data; the one-year gap in reporting; and the passive, hospital-based surveillance methods that may have missed cases outside this period, particularly among patients off-therapy, who were at lower risk for complications. Although we included off-therapy patients in our results, no off-therapy patient experienced a complication of varicella. Finally, the sample size limited our ability to define risk factors for morbidity in this setting. Interruptions in chemotherapy recorded as attributed to neutropenia and not to varicella, despite concomitant varicella infection, were not included, although varicella itself may cause prolonged neutropenia. In some cases, the interruption may have been initiated due to varicella and continued due to neutropenia, though the medical record may only have reflected one rationale.

In summary, varicella is a significant problem for children treated for cancer in Guatemala, with an incidence of 23.4 cases per 1000 p-y, a minimum cost of 598.75 USD per episode, and a 3.4% risk of death. This suggests the need for prophylactic strategies; however, failure to recognize exposures is a barrier to effective post-exposure prophylaxis. Further study of investigational inactivated vaccines is warranted to provide pre-exposure prophylaxis for previously unvaccinated children who are newly diagnosed with cancer. Prospective studies should thoroughly evaluate the cost-benefit of this approach.

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Competing interest: The authors declare no competing interest.

Contributors: BAEC designed study, wrote the protocol and developed data collection tool, extracted data from databases and original medical records, analyzed data and interpreted results, wrote the first draft and developed all tables, revised all subsequent drafts, reviewed and approved final version. AEJ conceived study, supported BAEC in designing and conducting study, interpreted study results, critically revised all drafts, including tables, reviewed and approved final version. MM assisted with data collection, critically revised drafts, and approved final version. AFA supported data collection, provided data for calculation of denominator, critically revised drafts, reviewed and approved final version. MP assisted with design of data collection tool, wrote statistical analysis plan, analyzed data, critically revised drafts, and approved final version. LMJ supported design of study, interpreted study results, critically revised all drafts, including tables, reviewed and approved final version.

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