Journal of Infection and Public Health (2016) xxx, xxx–xxx

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Chicken pox infection in patients undergoing chemotherapy: A retrospective analysis from a tertiary care center in India

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Received 29 August 2015; received in revised form 10 December 2015; accepted 19 December 2015

KEYWORDS
Chicken pox;
Chemotherapy;
Solid tumor cancers

Summary There is paucity of data on the incidence, severity and management of chicken pox in patients receiving active chemotherapy for cancer.

From October 2010 to October 2011, patients were included in this study if they developed a chicken pox infection during their chemotherapy. The details of patients' cancer diagnosis and treatment along with clinical and epidemiological data of the chicken pox infections were assessed from a prospectively maintained database.

Twenty-four patients had a chicken pox infection while receiving chemotherapy and/or radiotherapy. The median age of the patients was 21 years, and two-thirds of the patients had solid tumor malignancies.

Overall, eight (33%) patients had complications, six (25%) patients had febrile neutropenia, four (17%) had diarrhea/mucositis, and four (17%) had pneumonia. The median time for recovery of the infection and complications in the patients was 9.5 days (5–29 days), whereas for neutropenic patients, it was 6.5 days (3–14 days). The median time for recovery from chicken pox infections in neutropenic patients was 10 days (5–21 days), compared with 8.5 days (0–29 days) in non-neutropenic patients ($P = 0.84$). The median time for recovery from infections was 8.5 days in patients with comorbidities ($N = 4$), which was the same for patients with no comorbidities.

The clinical presentation and complication rates of chicken pox in cancer patients, who were on active chemotherapy, are similar to the normal population. The recovery from a varicella infection and complications may be delayed in patients with

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http://dx.doi.org/10.1016/j.jiph.2015.12.016

Please cite this article in press as: Noronha V, et al. Chicken pox infection in patients undergoing chemotherapy: A retrospective analysis from a tertiary care center in India. J Infect Public Health (2016), http://dx.doi.org/10.1016/j.jiph.2015.12.016

neutropenia. The varicella infection causes a therapy delay in 70% of patients. Aggressive antiviral therapy, supportive care and isolation of the index cases remain the backbone of treatment.

Introduction

The Varicella Zoster virus (VZV) is categorized as an alfagroup of a herpes virus family. Chicken pox is usually mild and associated with a rapid recovery in children. In India, children often acquire the infection at an early age and develop immunity against repeated attacks of chicken pox [1,2]. Seventy-two percent of the population between the ages of 15 and 25 years will have developed infections and seroconversion [1—3].

Immune suppression leads to severe, prolonged and disseminated chicken pox infections, with complications, including pneumonia, gastrointestinal, hepatic involvement, encephalitis and death [3,4]. Immune suppression in malignancies is multifactorial with common causes, including steroid use, chemotherapy, dysregulated immunity in hematolymphoid malignancies and bone marrow transplantation (BMT) [4]. There are several papers in the literature on herpes zoster and chicken pox infections in hematolymphoid tumors, especially in the BMT settings [4—6]. The immune suppression in solid tumor malignancies is not usually severe or prolonged, and recovery is possible within 2—5 days duration.

Both chicken pox and herpes zoster infections occur in solid tumor patients; there is however, a paucity of data on prophylactic acyclovir and varicella vaccine use, as well as a lack of data on the incidence, severity and treatment of chicken pox infections in patients with solid tumor malignancies on active chemotherapy. Hence, we retrospectively analyzed our database to assess the clinical spectrum, severity, complications and course of chicken pox infections in patients on active chemotherapy and to explore the role of vaccination and acyclovir prophylaxis in relatives of patients on active chemotherapy.

Materials and methods

Between October 2010 and October 2011, we retrospectively attempted to identify all of the patients receiving chemotherapy from the department of medical oncology who developed a chicken pox infection during their therapy. BMT patients and patients with herpes zoster infections were excluded.

Statistical analysis

Demographic data and detailed histories, examinations and laboratory parameters noted at diagnosis were recorded and assessed. Demographic data included age, gender, Eastern Cooperative Oncology Group performance status, comorbidities such as diabetes mellitus, the type of malignancy (solid tumors vs. hematolymphoid malignancy) and intent of chemotherapy and laboratory parameters at the time of patients' active infections. We elicited a detailed history of chicken pox in patients' relatives and surrounding people and a personal and past history of chicken pox. The laboratory abnormalities and complications at diagnosis were graded using the common terminology criteria for adverse events (CTCAE) version 4.03. The potential effect of various factors, such as the type of tumor (i.e., solid vs. hematological malignancy), the age of the patient (adult vs. pediatric) and the presence or absence of comorbidities on the duration of neutropenia and duration of recovery from chicken pox infection was calculated with Student's *t*-test for unpaired samples. A P value of <0.05 was considered statistically significant. Recovery from neutropenia was defined as an increase in the absolute neutrophil count (ANC) $\geq 1500\,\text{cmm}^{-1}$. Recovery from the chicken pox infection was defined as the patient

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Table 1 Demographic details.

Age ($n = 24$)	Median	21 years	Range	2—65 years
Gender ($n = 24$)	Males	15 (62%)	Female	9 (38%)
ECOG PS	0—1	24(100%)	≥2	0
Comorbidities	Yes	4 (16%)	No	20 (84%)
Past history of chicken pox (available in 13/24 patients)	Yes	3/13 (23%)	No	10/13 (67%)
History of chicken pox in family/surrounding people in past or same time (available in 13/24 patients)	Yes	11/13(84%)	No	2/13(16%)

being afebrile for 48 h and scabbing of the chicken pox rash.

Diagnosis of varicella infection (chicken pox)

The diagnosis was based on clinical evaluation of the lesions, specifically classic pleomorphic lesions at various phases of eruption, vesiculation and scabbing. Clinical photographs were used for documenting resolution of lesions. Serology was not used for diagnosis or follow-up. The diagnosis was confirmed in two patients with the DFA method on the scab scraping. Remaining cases were clinically confirmed cases with an epidemiological association with other confirmed or probable cases.

Therapy and complications

We assessed the therapy administered for the chicken pox infection and complications, including hospitalization, ICU admission, myelosuppression or organ failure. We also noted any delay in the planned therapy, including chemotherapy or radiotherapy as a result of the varicella infection.

Results

Demographic details

During the one-year period, we identified 24 patients with classical chicken pox infection while on treatment, including chemotherapy with or without radiotherapy. The majority of them were adults (median age 21 years), and two-thirds of the patients had solid tumor malignancies receiving curative intent neoadjuvant or adjuvant chemotherapy (Table 1).

Cancer diagnosis and treatment details

Fifteen (64%) of the patients were adult solid tumor patients (lung cancer: two, breast cancer: six, sarcoma: four, others: three); five patients (20%) were adult hematolymphoid (NHL: one, acute leukemia: four) and four (16%) were pediatric patients (leukemia: two, non-Hodgkin's lymphoma: one, sarcoma: one). All patients were on active first-line chemotherapy except one who was on second line chemotherapy. The intent of chemotherapy was curative in 20 (83%) patients. Twenty (84%) patients were on a triplet chemotherapy regimen.

Table 2 Hematologic parameters at the time of varicella infection.

Parameters	Median value	Range
Hb	10.95 gm/dl	(8.1—13.1)
WBC	$5.20 \times 10^9\,L^{-1}$	(0.3—12.1)
ANC	$3.30 \times 10^9\,L^{-1}$	(0.02—10.8)
Platelets	$218 \times 10^9\,L^{-1}$	(6—587)
Albumin	3.4 gm/dl	(2.6—4.4)

Presenting symptoms

All patients had a pleomorphic vesicular rash all over the body, especially on the trunk, which was diagnostic of chicken pox in all 24 (100%) patients. A high grade fever was observed in 16 (66%) patients. Eight patients (33%) had gastrointestinal symptoms, in the form of abdominal pain, diarrhea or vomiting. Three patients (13%) had respiratory complaints, such as a dry cough or breathlessness.

Hematologic parameters at the time of varicella infection

Twelve patients (50%) had neutropenia during the chicken pox infection; the severity was grade 3 in one patient and grade 4 in four patients (Table 2).

Complications

Eight (33%) patients had complications during the chicken pox infections. Six patients (25%)

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Table 3 Comparison between recovery from infection and neutropenia in patients with solid tumors vs. hematolymphoid and adult vs. pediatric patients.

Median duration in days	Solid tumors	Hematolymphoid malignancies	*P* value
For recovery from the infections	8.5 (3—21) *N* = 16	8.5 (6—29) *N* = 8	*P* = 0.34
Recovery from the neutropenia	7 (3—10) *N* = 8	7 (6—14) *N* = 3	*P* = 0.42
Median duration in days	**Adult patients**	**Pediatric patients**	***P* value**
For recovery from the infections	8 (3—21) *N* = 17	10 (5—29) *N* = 7	*P* = 0.45
Recovery from the neutropenia	7 (3—10) *N* = 7	7 (4—14) *N* = 5	*P* = 0.66

had febrile neutropenia; four (17%) had diarrhea/mucositis; and four patients (17%) had pneumonia, of which three were bacterial (consolidation with air bronchogram) and one was fungal pneumonia (fibronodular lesions with ground glass opacities) based on a CT of the thorax. One patient had central nervous system involvement in the form of convulsions, which were not related to high grade fever. He had developed intraparenchymal hemorrhage along with grade 3 myelosuppression required ICU admission, ionotropic support for hypotension, along with antifungals and third line antibiotics. None of the patients died of the complications related to their varicella infections.

Therapy for the varicella infection

Intravenous acyclovir was administered to 19 (79%) patients, and five (21%) patients were managed with oral acyclovir. The acyclovir course consisted of 14 days of the therapeutic dose of 10 mg/kg/dose administered three times a day, followed by oral secondary prophylaxis until the completion of chemotherapy. Admissions were required for 20 (84%) patients with isolation in an attempt to prevent the spread of the infection to the other patients in the hospital. Eight patients were given growth factor support as a part of managing the febrile or non-febrile neutropenia.

Clinical course and recovery

The median time for recovery of the infection and its complications in all patients was 9.5 days (5—29 days), whereas neutropenic patients recovered with a median duration of 6.5 days (3—14 days). The median time for recovery from chicken pox infections in neutropenic patients was 10 days (5—21 days), compared with 8.5 days (0—29 days) in non-neutropenic patients ($P = 0.84$). The median time for recovery from infections was 8.5 days in patients with comorbidities, which was the same for patients without any comorbidities. The comparison between recovery from infection and recovery from neutropenia in patients with solid tumors compared with hematolymphoid malignancies and adult vs. pediatric patients is shown in Table 3.

Effect of chicken pox on cancer-related therapy

Varicella infection caused a delay or omission of chemotherapy in 17 (70%) patients and in radiotherapy treatment of three (12.5%) patients. The median number of days of delay for chemotherapy or radiotherapy treatment was nine days (0—51 days).

Discussion

In India, most children are exposed to a varicella infection during early childhood [8]. Past clinical or subclinical infections demonstrated by a raised antibody level in the serum, provides protection from future chicken pox infections during periods of immunosuppression [8]. Treating a varicella infection and its complications in pediatric patients with leukemia and those undergoing BMT is a standard practice based on the recommended guidelines [9]. In regard to chicken pox in adult solid tumor malignancies, there are many questions that remain unanswered.

We report on 24 patients with chicken pox infections during active chemotherapy. The majority of the patients were adult patients with solid tumor malignancies and our results give some insight into this disease and its impact on the treatment of cancer. Our results also highlight many important aspects of chicken pox infections in solid tumor malignancies, which is scarce in the literature.

The clinical presentation in oncology patients did not seem to differ from those without malignancies. The complication rates were comparable to pediatric malignancies, such as pneumonia, that occurred in 16.5% in our cohort compared with 15—27% that was previously reported in

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pediatric malignancies [4]. There were no mortalities attributable to chicken pox infection, suggesting that aggressive antiviral therapy and supportive care are essential components for managing these patients.

The severity of disease or delay in recovery from the disease was not significantly different in any particular chemotherapy protocol, and the same is also true for hematological malignancy vs. solid tumor cancers. However, this may be due to the small numbers in our study.

Various factors such as the presence of comorbidities, neutropenia, type of malignancy (solid vs. hematolymphoid) and the age of the patient (adult vs. pediatric) did not appear to have any significant effect on the time taken to recover from a varicella infection. Although the median duration of neutropenia was the same in adults vs. pediatric patients, the median duration of recovery from varicella infection was numerically longer in pediatric patients compared with adults and in neutropenic patients compared with patients without neutropenia; however, these variables did not reach statistical significance. The small numbers in this study preclude any firm comment on these factors being significant.

We found that 70% of our patients had a delay (median of nine days) in chemotherapy as a result of varicella infection. Eighty-three percent of our patients were receiving therapy with the intent to cure. It is widely known that delays in curative treatment can lead to an inferior outcome, as has been studied extensively in breast cancer patients [10]. There is a clear need to prevent chicken pox infections effectively in cancer patients on active chemotherapy to ensure that these patients have the best possible outcome from therapy.

In our cohort, 84% patients had a past recent history of exposure to active chicken pox infection, with three of the patients staying in close proximity to each other. Only two of these 13 had developed childhood clinical chicken pox infection, while the remaining patients probably were unexposed to the varicella virus. Of note, there was no documented epidemic of chicken pox in Mumbai during the period of our analysis. None of the patients' relatives had received varicella vaccines and no patient was offered prophylactic acyclovir after the diagnosis of chicken pox in the relatives.

As a result of an overall improvement in socioeconomic status, the age of exposure to varicella infections in Indian patients is shifting to the adult age. The varicella infection in an adult is much more severe compared with childhood varicella infections. This fact, combined with the immunosuppression due to chemotherapy for malignancies, probably contributed to the complications and therapy delays in our patients. We need to consider implementing a vaccination program for relatives, even in adult solid tumor cancer patients. There are many recommendations for sibling vaccinations and child vaccination during the maintenance therapy in ALL [11,12], which needs additional consideration in adult solid tumor malignancies.

The safety of the chicken pox vaccine in children with hematological malignancies, who are on active chemotherapy, is controversial [13,14]. Non-immune children with cancer can be effectively vaccinated against chicken pox during the maintenance phase of their acute leukemia treatment or approximately three to six months from treatment discontinuation in those with solid tumors [15]. In clinical trials, transmission of the vaccination version of the virus to immune-compromised contacts from vaccine recipients is not reported, but a possible transmission can occur rarely from vaccine recipients who develop a varicella-like rash [16].

Isolation is another major tool in preventing the spread of infection. We used isolation for the inpatient management of the active chicken pox patients; this strategy likely helped in preventing the spread and possible chicken pox outbreak in our center, which caters to approximately 54,000 cancer patients per year. Isolation of an actively infected chicken pox patient in a negative pressure room is recommended by the American Academy of Pediatrics [17]. If negative air-flow rooms are not available, patients with varicella should be isolated in closed rooms and have no contact with persons without evidence of varicella immunity; patients should only be cared for by staff with varicella immunity. Pediatric oncology units have begun to implement isolation measures after the emergence of reports of chicken pox infection outbreaks in wards [18].

To summarize, the clinical presentation and complication rates of chicken pox in cancer patients who were on active chemotherapy are similar to the normal population. The recovery from a varicella infection and complications may be delayed in patients with neutropenia. The varicella infection causes a therapy delay in 70% of patients. Aggressive antiviral therapy, supportive care and isolation of the index cases remain the backbone of treatment.

Our data had a small number of patients and was a retrospective analysis. Patients were randomly selected and the patient group was heterogeneous, including both adult and pediatric patients with solid tumors or hematolymphoid malignancies. A strength of our analysis includes the fact that it describes the complications of a chicken pox

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infection in patients with malignancies receiving active therapy. It also discusses the differential effects of neutropenia, tumor type, age of patients and the presence of comorbidities on the patients' ability to recover from a chicken pox infection. This paper describes the delays in chemotherapy and radiotherapy treatment due to a varicella infection. Most importantly, the inclusion of adult solid tumor patients and the descriptions of their clinical courses and complications when they develop a varicella infection while on active anti-tumor therapy is unique.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

Acknowledgements

None declared.

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