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Research Article

Rhinovirus Infection Associated Cytopenias during Maintenance Phase in Children with Acute Lymphoblastic Leukemia

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Abstract

Respiratory infections are a common cause of cytopenias in pediatric cancer patients undergoing treatment, with rhinovirus being the most frequent culprit. We aimed to assess the impact of rhinovirus infections during long-term, low-intensity chemotherapy maintenance in children with acute lymphoblastic leukemia. Clinical characteristics and outcomes of patients infected with rhinovirus between 2011-2021 were analyzed. Of the 207 patients on maintenance, 22% presented rhinovirus infection, with 50% experiencing associated cytopenia leading to treatment interruptions in 37% of patients. No increase in relapses or mortality was observed.

These findings suggest that rhinovirus infections can cause bone marrow toxicity during maintenance treatment of acute lymphoblastic leukemia. Thus, the screening for rhinovirus infection should be considered as part of the investigation in cases of unexpected pancytopenia during maintenance treatment.

Keywords: Rhinovirus, Cytopenia, Maintenance, Acute Lymphoblastic Leukemia, Children, Pediatric

Abbreviations: ALL: Acute Lymphoblastic Leukaemia; BMA: Bone Marrow Aspirate; HB: Haemoglobin; M1: Maintenance 1; M2: Maintenance 2; NPA: Nasopharyngeal aspirate; PCR: Polymerase chain reaction; PETHEMA: Programa Español de Tratamientos en Hematología; RNA: Ribonucleic Acid; RV: Rhinoviruses; SD: Standard deviation; SEHOP: Sociedad Española de Hematología y Oncología Pediátrica; VRTI: Viral Respiratory Tract Infection

Introduction

Despite increased survival rates for pediatric cancer, infections remain a major complication. Community-acquired Viral Respiratory Tract Infections (VRTIs) are associated with

increase of morbidity and mortality, and delays in chemotherapy [1]. Rhinoviruses (RV) are the most common causative agents.

The clinical presentation of VRTI is nonspecific and depends on patient characteristics such as the underlying disease, chemotherapy and immunosuppression [2,3].

Rhinoviruses are RNA viruses that circulate year-round, with seasonal peaks. Clinical presentation is variable, with most of the patients presenting with upper VRTI. Immunocompromised patients may have prolonged viral shedding, being challenging to interpret a single positive PCR detection as the causative agent of an actual infection [5].

Patients with acute lymphoblastic leukemia (ALL) are expected to present mild neutropenia with normal hemoglobin and platelet count during the maintenance phase due to non-intensive chemotherapy regimen[1]. Cases of cytopenias in the context of acute respiratory viral infections in heterogeneous groups of pediatric cancer have been reported [3]. These patients may need hospital admission, antibiotics, or withdrawal of maintenance chemotherapy.

To determine the impact of RV on the management of patients with ALL and mild-intensity chemotherapy, such as the maintenance cycle, we studied the association between RV infection and cytopenias, as well as the suspension of chemotherapy and the outcome of this group of patients.

Methods

This was a retrospective observational study conducted at the Department of Pediatric Oncology and Hematology of the Vall d'Hebron Hospital, a tertiary hospital in Barcelona (Catalonia, Spain). The local Ethics Committee for Clinical Research approved the study in January 2023 (PR (AMI) 42/2023).

Patients Selection and Data Collection

Consecutive symptomatic episodes of RV detection in ALL pediatric patients (< 18 years) in the maintenance phase were included from January 2011 to December 2021. Episodes due to a second positive detection in less than one month were excluded as considered due to prolonged viral shedding. Electronic medical records were reviewed for epidemiological, clinical and microbiological data. Patients were treated according to the LAL-SEHOP-PETHEMA-2013 protocol with M1 referring to oral methotrexate, mercaptopurine and asparaginase plus intrathecal triple therapy and M2 to oral methotrexate and mercaptopurine.

Definitions

An episode was defined as a positive result in the Nasopharyngeal Aspirate (NPA) for RV in symptomatic patients without a previous positive test within the last month. Neutropenia was defined as absolute neutrophil count of <1500 cells/ μL and severe neutropenia of <500 cells/μL. Anemia was considered to be present if the hemoglobin (Hb) was below the lower limit of 2 Standard Deviations (-2SD) for the normal population. Thrombocytopenia was defined as a count of <100000 platelets/ μL. Hematological toxicity was evaluated considering the presence of cytopenias, severity, duration and the need for transfusion.

Procedures

Rhinoviruses and other respiratory viruses were detected in respiratory specimens by using a multiplex one-step real-time RT-PCR assay (Allplex Respiratory Panel, Seegene, South Korea). Hematological counts were registered from the same day of the NPA and from previous blood tests to determine each patient's baseline values.

Statistical Analysis

Descriptive analysis was performed using frequency of distributions and means. To compare proportions, a $\chi 2$ test was performed. IBM SPSS Statistics® for Windows, Version 25.0. Armonk, NY IBM Corpv was used.

Results

Patient's characteristics

During the study period, 207 pediatric ALL patients in the maintenance phase were treated at our center. Out of these, 46 patients (22%)-with a mean age of 5.8 years and SD of 3.17-experienced 61 episodes of RV infection (7 patients had more than one episode during maintenance therapy). Forty-six percent of the episodes occurred during M1 while 54% during M2. Regarding the type of ALL treatment stratification, 70% were an intermediate risk, while 28% and 2% were in patients with high and standard risk respectively.

Rhinovirus infection

Most infections (75%) occurred between September and February, with the highest incidence in October (31%). Fever (14.7%), common cold (34.4%) and the combination of both (36%) were the most frequent symptoms. One patient presented a lower VRTI (1.6%).

Of all episodes, 34% required hospital admission. Antibiotics (intravenous or oral) were administered in 52.4% and 1.6% required oxygen supply. Co-infection was identified in 19.6% episodes (Table 1).

	No (%)
Human parainfluenza virus type 3 (HPIV-3)	2 (3.2)
Human parainfluenza virus type 4 (HPIV-4)	1 (1.6)
Respiratory syncytial virus	3 (4.9)
Adenovirus	1 (1.6)
Human metapneumovirus	1 (1.6)
Enterovirus	1 (1.6)
Proteus mirabilis (*urine culture)*	1 (1.6)
Streptococcus pneumoniae (*blood culture*)	1 (1.6)
Escherichia coli (*blood culture)*	1 (1.6)
No co-infection	49 (80.3)
(*) detections performed in nasopharyngeal aspirate except for those where another source is provided.	

Table 1: Laboratory-confirmed co-infections in the 61 clinical episodes reported during the study period (*).

Hematological complications

Fifty percent of episodes were associated with at least one new cytopenia. Among patients with a decrease in their hemoglobin values, 86% had a value in the range for anemia. Regarding the drop in the platelet level, 35% achieved levels below 100.000 platelets/μL. About the decrease in the neutrophil count, 96% were in the range for neutropenia, being severe in 23% of them.

To rule out confusion factors, type of maintenance and co-infection were analyzed in relation with cytopenia incidence. No statistically differences were found, neither with chemotherapy regimen (M1 46% vs. M2 54%, p value 0.157) nor co-infection (co-infection 58.3%, no co-infection 48.9%, p value 0.560).

A delay in chemotherapy occurred in 32.7% with a median duration of the treatment withdrawal of 7 days (IQR 4). Bone marrow aspiration (BMA) was performed in 8.1% due to prolonged cytopenia, and immunophenotype ruled out relapse. There were two relapses, both in patients without treatment withdrawal. No microbiological studies were performed. No deaths were recorded.

Complete data is summarized in Table 2.

	Cytopenia No (%)	Initial values	Median decrease	Nadir values during infection	Median days to recover (IQR)	BP transfusion No (%)
Decrease in Hb values	21 (34.4)	11.76 g/ dl±1.33SD	1.96 g/dl ±1.08 SD[1]	9.7 g/dl ± 1.86 SD	4.5 (5.7)	5 (23)
Anemia (-2DE)	18/21 (26)					
Decrease in Neutrophil count	27 (44.2)	2248 /mcl ±1428 SD	1823 /mcl ±1621 SD	677/mcl ±574 SD	7.5 (28)	NA
SN (<500/mcl)	14/27 (22.9)	-	-	-	-	-
Neutropenia (<1500/cmcl)	26/27 (96)	-	-	-	-	-
Decrease in platelet count	17 (27.8)	185764 /mcl ±85752 SD	79941 /mcl ±66148 SD	105823 /mcl ±69581 SD	6 (7)	1 (5.8)
Thrombocytopenia (<100000)	6/17 (21)	-	-	-	-	-
At least one cytopenia	32 (52.4)	-	-	-	-	-
BP: blood products; NA: not applicable; SD: standard deviation; SN: severe neutropenia						

Table 2: Summary of cytopenias occurred in the 61 clinical episodes reported during RV infection.

Discussion

In our study, children with ALL and RV infection presented with a mild disease, but cytopenias were common and led to increased chemotherapy delays. Nonetheless, no relapses were detected in these patients.

Many publications report the impact of viral infections in hematological patients 3, 5, but little is known concerning the association between RV infection and aplasia. The few previous reports showed a similar rate of RV laboratory-confirmation, ranging from 30% to 76%5. Data on co-infection is consistent with previously published studies (19-20%) 3, 5.

In our study, cytopenias were detected in 52.4% of cases, and 44.2% presented with a low neutrophil count. This was in line with Aydın Köker et al study[3], which reported a 42% rate of neutropenia associated with RV infection and a 33% rate of chemotherapy delays compared to our 32.7%.

Other causes of aplasia (asparaginase use and co-infections3) were not related to its incidence, suggesting that RV infection may be an independent risk factor for aplasia.

Treatment continuity during maintenance has a significant impact on its response, so delays should be avoided8. Despite this, we did not find any relapse events during the follow-up of patients in whom chemotherapy was discontinued in relation to RV-related cytopenias.

This study has some limitations. It is a retrospective, single-center study that may limit data collection, but our electronic medical record minimizes potential loss of information. The use of a single-point PCR RV detection may incorrectly preclude RV as the cause of infection in a population with prolonged viral shedding. To minimize this, we excluded those with a recent detection. The fact that the study ends in December 2021 could cause some detection bias since NPAs were more commonly performed from March 2020 due to the COVID-19 pandemic. Lastly, RV testing was not performed in BMA to rule out a direct cytopathic virus effect.

In conclusion, in our series, RV infection during maintenance treatment was frequent, causing cytopenias in half of the patients and delays in chemotherapy in one out of three, without increasing the risk of relapse. Thus, screening for rhinovirus infection should be considered as part of the investigation in cases of unexpected pancytopenia during maintenance treatment, particularly during the colder months.

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