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Respiratory Syncytial Virus Infections in Children with Acute Myeloid Leukemia: A Report from the Children's Oncology Group

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Abstract

Background—Morbidity and mortality related to respiratory syncytial virus (RSV) in pediatric acute myeloid leukemia (AML) is not known.

Procedure—We combined data from three Children's Oncology Group AML studies and determined the prevalence of RSV infection and RSV-related mortality in children treated for *de novo* AML.

Results—We found that the prevalence of RSV infection ranged from 0-1% in induction and between 0.3-2.2% in consolidation. Four children died from RSV resulting in RSV-specific mortality of 0.2% among all children. However, the risk of RSV-related mortality among RSV infection episodes was high (4/40, 10%).

Conclusions—RSV infections and deaths are rare in pediatric AML.

Keywords

Respiratory Syncytial Virus; Acute Myeloid Leukemia; Children

INTRODUCTION

Respiratory syncytial virus (RSV) is a common cause of infection in immunocompetent and immunocompromised hosts. Immunoglobulin against RSV has been suggested to reduce morbidity of infection in some high risk hosts. More specifically, guidelines from the American Academy of Pediatrics (AAP) recommend that either intravenous RSV immune globulin (RSV-IGIV) or palivizumab, a humanized monoclonal immunoglobulin, be considered for infants and children younger than 2 years of age with chronic lung disease who require medical therapy and those born at 32 weeks gestation or earlier.[1] The AAP

also suggests palivizumab for children with hemodynamically significant congenital heart disease. For these patients, the AAP suggests that prophylaxis be initiated soon after the onset of RSV season and continue until the end of the RSV season, usually November until March in northern hemispheric countries. The recommendations note that prophylaxis has not been evaluated in randomized trials in immunocompromised children although those with severe congenital or acquired immunodeficiency may benefit.

Among children with cancer, those receiving treatment for acute myeloid leukemia (AML) are among those who experience the most profound and prolonged leukopenia. Thus, these children are an important group to consider for prophylaxis with RSV immunoglobulin. However, palivizumab is costly and it would be important to know the burden of RSV infection and mortality in this population in order to guide recommendations. Almost no data were available in the literature upon which to base such recommendations. Thus, we undertook a retrospective review of three large cooperative group AML trials from which this information could be ascertained. The objectives of this report were to describe the prevalence of RSV infection and RSV infection-related mortality in children with AML.

METHODS

Patients and Methods

The data set included children enrolled onto three AML trials of the Children's Oncology Group, namely AAML03P1, CCG-2961 and CCG-2891. Only patients with *de novo* AML were included in this analysis. These studies were approved by each participating institution's review board. Informed consent was provided according to the Declaration of Helsinki.

AAML03P1—Therapy consisted of daunorubicin, cytarabine and etoposide for cycles 1 and 2 followed by cytarabine and etoposide for cycle 3, mitoxantrone and cytarabine for cycle 4, and cytarabine and L-asparaginase for cycle 5. Gemtuzumab ozogamicin was given in cycles 1 and 4. Patients with a matched family donor (MFD) were assigned to allogeneic stem cell transplantation (SCT) after cycle 3. This study accrued 341 patients from December 2003 to October 2005.

CCG 2961—Therapy consisted of four phases: (1) Induction (idarubicin, daunomycin, cytarabine, thioguanine, etoposide, and dexamethasone (IdaDCTER)); (2) Consolidation, (randomization between a second IdaDCTER cycle versus fludarabine, cytarabine, and idarubicin); (3) Intensification (cytarabine and L-asparaginase or allogeneic SCT for those patients with a MFD); and (4) Immune Modulation, (randomization to interleukin-2 or none in patients without donors after phase 3).[2] This trial accrued 901 patients between August 1996 and December 2002.

CCG 2891—Induction consisted of four cycles of a five-drug regimen of chemotherapy: dexamethasone, cytarabine, thioguanine, etoposide and daunorubicin (DCTER), either administered as intensive or standard timing. Those in remission after four DCTER cycles with a MFD were allocated to allogeneic SCT. All others were randomized between autologous SCT and intensive chemotherapy (cytarabine and L-asparaginase). Consolidation chemotherapy consisted of four courses of three chemotherapy regimens.[3,4] This trial accrued 836 patients between October 1989 and May 1995.

For all this analysis, data regarding RSV infections were sought only during phases of chemotherapy and not SCT. For CCG 2961, only RSV infections during chemotherapy phases 1-3 were included. For all trials, specific recommendations regarding RSV were not made and management was left to the clinician's discretion.

Determination of RSV Infection and Infection-Related Mortality

RSV infections were identified either from the infection case report form or the toxicity case report form depending on the specific trial. For those enrolled on AAML03P1 or CCG 2891, date of RSV infection was available. For these studies, we classified potential RSV-related deaths as infection-related mortality in which RSV infection was documented within 30 days of death. However, for CCG 2961, date of RSV infection was not recorded and only phase of therapy in which RSV infection occurred was available. Thus, for this study, we classified potential RSV-related deaths as infection-related mortality in which RSV infection occurred in the same phase of therapy in which death occurred. Mortality attributable to RSV was confirmed through review of autopsy reports and the studies' death registration forms.

The prevalence of RSV infection in each phase of therapy was defined as the number of children with at least one RSV infection divided by the number of children starting that phase of therapy. RSV infection mortality was expressed as the number of children who died from RSV divided by the total number of eligible children with *de novo* AML enrolled on the trials.

Examination of RSV prevalence does not account for the seasonal nature of infection. Given that the vast majority of children enrolled on COG studies live in the northern hemisphere, we also examined the occurrence of RSV and the proportion of RSV infections among those who were infected and received at least one day of induction or consolidation chemotherapy between November 1 and March 31. We also examined the prevalence of RSV mortality among children who died and received any chemotherapy during this same time frame.

RESULTS

The number of patients enrolled onto AAML03P1, CCG 2961 and CCG 2891 are displayed in Table 1; in total, 2,078 eligible children were registered on these trials. Among these three studies, the prevalence of RSV infection ranged from 0 to 1% for children in induction and between 0.3 and 2.2% in consolidation. In total, there were 40 RSV infections experienced by these children. Table 1 illustrates the ages of all children and those who developed RSV infection. If one accounts for only those at risk during RSV season, then the prevalence of RSV infection between November 1 and March 31 ranged from 0 to 2.2% in induction and between 0.6 and 2.5% in consolidation (data not shown). Six children (all treated on CCG 2961) did not have RSV infections between November 1 and March 31. One patient had RSV infection in all phases of therapy with one phase occurring within this time frame and the other two phases occurring outside of this time frame. All these RSV infections occurred in northern hemispheric institutions.

Table 1 also illustrates the number of potential RSV deaths on each of these studies. In total, four children died from RSV during these three AML trials; all four RSV-related deaths were confirmed by the death registration form review. Three were male and one was female. The ages of these four children were 3, 9, 23, and 25 months. The one RSV death on AAML03P1 occurred during intensification III while the three RSV deaths on CCG 2961 occurred during induction (Phase I).

When examining all enrolled children, the risk of RSV infection-related mortality was 4/2,078, 0.2%. If only those less than one year of age are examined, the risk was 2/219, 0.9% while for children < 2.5 years of age, the risk was 4/520, 0.8%. One RSV death occurred outside of the RSV season in a northern hemisphere institution. The prevalence of RSV-related mortality among those receiving chemotherapy during the RSV season was

0.2%. For all age groups, the risk of RSV-related mortality among RSV infection episodes was 4/40 (10%).

DISCUSSION

We found that the prevalence of RSV infection in children undergoing chemotherapy for AML is low during induction and consolidation chemotherapy and that RSV infection may contribute to death in 0.2% of children. While RSV infection may have been underreported, it is unlikely that deaths from RSV would not have been reported. Thus, our estimate of 0.2% risk of RSV infectious deaths likely is accurate.

We do not believe prophylactic palivizumab is routinely indicated in children with AML because the baseline risk of RSV infection is low. In contrast to the maximal prevalence of RSV infection of 1% to 2% among different AML trials, the prevalence of RSV infection is higher among at least some high-risk populations. Among six randomized studies of immunoglobulin or palivizumab prophylaxis in children with prematurity, chronic lung disease or congenital heart disease, the prevalence of RSV infection or RSV hospitalization in the control arms ranged from 9.7% to 30.8%. [5-10] Additional reasons that we believe routine prophylactic palivizumab should not be used are because reduction in hospitalization related to RSV (major benefit in non-cancer trials) is unlikely to impact on this population and RSV immunoglobulin prophylaxis does not reduce mortality. [5-10] In addition, three deaths were in induction and one death occurred outside of RSV season, which further reduces the probability that prophylaxis can impact on RSV-related mortality.

It is important to distinguish between strategies to prevent and treat RSV infection. While our data do not support routine administration of palivizumab to prevent RSV infection, 10% of RSV episodes were associated with RSV-related deaths. The mortality rates among the other high risk children included in the previously mentioned six randomized trials were lower, with mortality rates in the control arms of 0 to 6.3% among the children with RSV infection or RSV hospitalization. [5-10] Thus, effective strategies to treat RSV infection are an important priority in pediatric AML. The usefulness of palivizumab for treatment of established infection is uncertain. [11]

Our report is limited as we did not have information regarding severity of RSV infection. In addition, rapid testing for RSV may not have been available in earlier study patients, which may have affected RSV prevalence estimates. Furthermore, while palivizumab prophylaxis does not reduce mortality in other high risk populations, we do not have any direct evidence about a possible effect on mortality in children with AML. However, the rarity of RSV infection in AML would preclude a randomized trial to definitively determine any effect on mortality within our population.

In conclusion, the risk of RSV infection in pediatric AML patients is low and RSV infection contributes to mortality in 0.2% of all children. However, children with AML who experience RSV infections are at high risk of RSV-related mortality.

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TABLE I

RSV infections and deaths on AAML03P1, CCG 2961 AND CCG 2891

	AAML03P1	CCG 2961	CCG 2891	Total
Characteristics of All Patients				
Included	De novo	De novo	De novo	De Novo
No. Total Patients	341	901	836	2,078
No. Patients				
< 1 year of age	39	101	79	219
< 2 years of age	78	193	177	448
<2.5 years of age	86	227	207	520
Median age (years)	9.5	9.5	7.6	8.7
Characteristics of Patients with RSV				
No. Subjects with RSV	6	25	4	35
Infections				
Median Age (Range) of those with RSV in Years	6.7 yrs (0.76 – 17.99)	2.1 yrs (0.24 – 16.82)	4.9 yrs (0.68 – 16.21)	2.2 yrs (0.24 – 17.99)
No. with RSV by Age				
< 1 year of age	1	5	1	7
< 2 years of age	1	12	2	15
< 2.5 years of age	1	16	2	19
No. Subjects with RSV Infections November 1 to March 31	6	19	4	29
No. Died of RSV*	1	3	0	4
Percentage of All Treated Patients Who Died of RSV	0.3%	0.3%	0%	0.2%

* Defined as deaths within 30 days of RSV infection or deaths in the same phase of therapy in which the cause of death was attributed to infection.