

Respiratory syncytial virus infection in infants with acute leukemia: a retrospective survey of the Japanese Pediatric Leukemia/Lymphoma Study Group

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Abstract Respiratory syncytial virus (RSV) can cause life-threatening complications of lower respiratory tract infection (LRTI) in young children with malignancies, but reports remain limited. We performed a retrospective nationwide survey to clarify the current status of RSV disease among infants with hematological malignancies. Clinical course, treatment, and outcome of patients with hematological malignancies who suffered from RSV infections at the age of <24 months during anti-tumor therapy from April 2006 to March 2009 were investigated by sending a questionnaire to all member institutions of the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG). Twelve patients with acute leukemia were identified as having experienced RSV disease. The primary diseases were acute myeloid leukemia ($n = 8$) and acute lymphoblastic leukemia ($n = 4$). RSV infection occurred pre- or during induction therapy ($n = 8$) and during consolidation therapy ($n = 4$). Eight patients developed LRTI, four of whom had severe

pneumonia or acute respiratory distress syndrome; these four patients died despite receiving intensive care. In our survey, the prognosis of RSV disease in pediatric hematological malignancies was poor, and progression of LRTI in particular was associated with high mortality. In the absence of RSV-specific therapy, effective prevention and treatment strategies for severe RSV disease must be investigated.

Keywords Respiratory syncytial virus · Acute leukemia · Infants

Introduction

Survival rate of children with pediatric hematological malignancies has improved dramatically in the recent years [1]. Not only the development of effective anti-tumor therapies, management of infectious complications, either bacterial, fungal, and/or viral, is also critical to maintain and to further improve their prognoses.

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Respiratory syncytial virus (RSV) is a common cause of lower respiratory tract infection (LRTI) mostly in young children, especially in infants [2, 3]. In healthy individuals, RSV generally causes mild and self-limited upper respiratory tract infections (URTI) only. However, in young children, especially those with malignancies undergoing cytotoxic chemotherapy, RSV could cause severe LRTI and is one of the most life-threatening pathogens among all the pathogenic viruses.

Most infants experience initial infection with RSV before the age of 2 years, however, permanent immunity cannot be acquired [4]. The frequency of recurrent infection is high regardless of age, and patients with immunodeficiency are at highest risk of fatal complications. Several reports have suggested that the prognosis of RSV disease in hematological malignancies is poor [5–9]. It has been reported that the mortality rate was high among infants with acute myeloid leukemia (AML) enrolled in the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) AML-05 study, and one of the causes was respiratory complication caused by RSV infection [10]. Because RSV-specific therapy is not yet established, progression of RSV-induced URTI to LRTI is associated with high mortality [6, 9]. A recent study of high-risk pediatric patients, including those with malignancies, noted 12.5 % mortality rate following RSV infections [6, 11].

We, therefore, retrospectively investigated data related to the clinical course, prognosis, and follow-up of RSV disease in Japanese infants with hematological malignancies.

Patients and methods

The subject of this retrospective study was patients with newly diagnosed acute leukemia or lymphoma, and those who suffered from RSV infection at the age of 24 months or younger during curative therapy for their malignant conditions. The survey period of the RSV-infection occurrence was 3 years from April 2006 to March 2009. RSV infection had to be confirmed by rapid RSV testing by immunochromatographic analysis of rhinopharyngeal swabs along with URTI and/or LRTI symptoms. The presence of applicable patients was confirmed in the primary survey, and information on demographics, laboratory and clinical data, treatment, and outcome were collected for all the subject cases in the secondary survey. These data were collected by questionnaire sent to all 180 centers across the nation that joined the JPLSG studies for the primary survey and selected centers with applicable cases for the secondary survey. The present research was approved by the Institutional Review Board of Fukuoka University Hospital and by the steering committee of the JPLSG.

Results

From the primary survey, we were able to obtain the information from 148 of the 180 JPLSG institutions (82 %). Sixteen cases from the 12 institutions were identified, but 4 cases were excluded from the present analysis because of the following reasons: three were aged older than 24 months at RSV infection and RSV infection was not confirmed by the appropriate RSV testing in one case. As a result, the remaining 12 cases were further analyzed. Patient characteristics are shown in Table 1.

All patients were positive for RSV antigen testing of rhinopharyngeal swabs. Median age at RSV infection was 10 months (range 2–21 months). There were seven boys and five girls. The primary diseases of the 12 patients were all acute leukemia: acute lymphoblastic leukemia (ALL, $n = 4$) and AML ($n = 8$). Patients #11 and #12 had trisomy 21 without heart disease or other complications. No patients had received palivizumab prophylaxis. The timing of RSV disease onset was September to November in eight cases and December to February in four cases.

Two patients (Patients #1 and #6) developed RSV disease before the initiation of induction chemotherapy, which was postponed until the respiratory symptoms had resolved (4 and 29 days, respectively). As a result, these two survived without severe complications. In the remaining ten patients, RSV infection developed during induction therapy in six cases and during consolidation therapy in four cases.

Most common symptoms were cough ($n = 12$) and fever ($n = 10$). In patients with URTI alone (Patients #1, #3 and #7), symptoms resolved within 4–11 days. Other nine patients developed LRTI with symptoms such as wheezing, tachypnea, and retraction (Patients #2, #4–6, and #8–12), and their median disease duration was 28 days (range 11–52 days). Four patients (Patients #4, #8–10) developed severe bronchiolitis, pneumonia, or acute respiratory distress syndrome (ARDS) after 10–39 days, which were all fatal in spite of intensive care including mechanical ventilation. Other complications such as acute myocarditis or encephalopathy were not encountered.

Laboratory data at onset of RSV disease are described as follows. Mean serum C-reactive protein (CRP) level was 0.81 mg/dL (range 0.03–2.64 mg/dL), and immunoglobulin (Ig) G values were ≥ 500 mg/dL (range 518–1055 mg/dL) in all patients. Peripheral white blood cell count was $\leq 1000/\mu\text{L}$ (range 100–700/ μL) in six patients and the lymphocyte count was $\leq 500/\mu\text{L}$ (range 0–476/ μL) in seven patients. Treatment after RSV infection involved intravenous infusion of antibiotics in 11 patients (excluding Patient #1), for a median period of 21 days (range 11–66 days). Oxygen administration was used in eight of nine patients with LRTI: four of these patients survived

Table 1 Characteristics, treatment, and outcome of the 12 infants who suffered from RSV disease

Sex	Primary disease	Age at onset of RSV disease (month)	Chemotherapy regimen (phase)	Symptoms	Diagnosis	WBC at onset ($10^9/L$)	ANC/lym at onset of RSV disease ($10^9/L$)	IgG at onset of RSV disease (mg/dl)	Steroid	IVIg	Anti-viral therapy	Oxygen administration	Outcome
1	F	ALL	13	MLL03 (pre-induction)	Cough, fever	URTI	117.8	518	No	No	No	No	Recovered
2	F	ALL	2	MLL03 (induction)	Cough	Bronchitis	0.1	553	No	No	No	Yes	Recovered
3	M	ALL	8	MLL03 (induction)	Cough, fever	ARDS	1.2	845	Yes	Yes	Palivizumab/rivabirin	Yes	Died (RSV infection)
4	M	ALL	21	JACLS HR02 (consolidation)	Cough, nasal discharge	URTI	0.2	689	No	Yes	No	No	Recovered
5	F	AML	11	AML-05 (induction)	Cough, fever	Bronchitis	1.6	785	Yes (pulse)	Yes	Palivizumab	Yes	Recovered
6	M	AML	4	AML-05 (pre-induction)	Cough, fever	Pneumonia	23.3	1055	Yes	Yes	Palivizumab	Yes	Recovered
7	F	AML	20	AML-05 (consolidation)	Cough, fever	URTI	0.1	618	No	Yes	No	No	Recovered
8	M	AML	7	AML-05 (induction)	Cough, fever	ARDS	1	668	Yes	Yes	No	Yes, MV	Died (RSV infection)
9	M	AML	7	AML-05 (pre-induction)	Cough, fever	Pneumonia	7.8	844	Yes (pulse)	Yes	Palivizumab	Yes, MV	Died (RSV infection)
10	M	AML	14	CCLSG AML9805RE (induction)	Cough, fever	Bronchitis	1.5	567	Yes (pulse)	Yes	No	Yes, MV	Died (RSV infection)
11	M	AML	17	AML99D (consolidation)	Cough, fever	Bronchitis	0.1	592	No	Yes	No	No	Recovered
12	F	AML	9	AML99D (consolidation)	Cough, fever	Bronchitis	0.7	538	Yes	Yes	No	Yes	Recovered

ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, ANC absolute neutrophil count, ARDS acute respiratory distress syndrome, F female, IVIG intravenous immunoglobulin, lym lymphocyte, M male, MV mechanical ventilation, NR not recorded, URTI upper respiratory tract infections, MLL03 The JPLSG trial for MLL-gene-rearrangement positive infantile ALL of the JPLSG [19], JACLS HR02 The Japan Association of Childhood Leukemia Study (JACLS) trial for high risk pediatric B-precursor ALL, AML-05 The JPLSG study for pediatric AML, CCLSG AML9805RE The Children's Cancer and Leukemia Study Group (CCLSG) trial for refractory pediatric AML, AML99D The Japanese AML cooperative study group trial for patients with Down syndrome (DS) and AML [20]

and their symptoms improved after 14–52 days of oxygen administration, while the other four patients did not survive despite receiving intensive care including mechanical ventilation, high-dose steroid treatment, etc.

Discussion

RSV is one of the most important respiratory viruses causing severe infections in patients with hematological malignancies. Previous reports showed that the occurrence of RSV infection during AML chemotherapy was about 10 %, and the RSV-associated mortality rate was 0.2 % [6, 10]. In our survey, RSV occurred in 12 patients, and 4 of the 12 patients died from RSV infection. This suggested that the prognosis was also poor in our study population.

RSV infection occurred most frequently during the induction phase ($n = 8$), which was the case in all the four fatal cases. Two patients were diagnosed with RSV infection prior to treatment and their induction chemotherapy was postponed until the symptoms had resolved: serious complications did not occur in these patients (Patients #1 and #5). It is therefore important to consider postponing chemotherapy in patients who are diagnosed with RSV infection prior to starting chemotherapy.

High mortality rate has been reported in cases with hematological malignancies complicated by RSV infection [5–7, 12]. In particular, the mortality rate was 50 % or higher for patients in whom disease status progressed from URTI to LRTI [6, 11]. Various reports have shown that progression to LRTI is an important prognostic factor [6, 11, 12]. In our study, symptoms improved within approximately 10 days in the three patients who only had upper respiratory symptoms. Nine patients had LRTI. Four of them developed severe pneumonia or ARDS and did not survive despite receiving intensive care including mechanical ventilation. Four of the five surviving patients required several weeks of oxygen administration. Other reported risk factors are aged under 3 years, old age, and lymphocytopenia [6, 7, 13, 14]. In our study, lymphocytopenia was detected in seven patients (58.3 %).

Effective treatment for RSV infection has not been established yet [6, 7, 13, 14]. Although efficacy has not been confirmed, steroids are often used to manage RSV infection. In our study, steroids were used in seven patients with progressive LRTI, although symptoms were not improved in any of these patients. Moreover, steroid pulse therapy was administered in four of these patients, and three of them died. Although many institutions used intravenous immunoglobulin therapy aiming an antiviral effect, no obvious effect could be seen in our series. Use of palivizumab, anti-RSV humanized monoclonal antibody, is

established for preventing severe RSV infections for young children with congenital heart disease, with history of premature infancy, and/or with history of bronchopulmonary dysplasia. In the current study, no patients underwent prophylaxis with palivizumab, but four patients received palivizumab for treatment after developing severe respiratory failure, and symptoms improved in two of them. This finding suggests the effect of palivizumab as a potential treatment choice and warrants for evaluation in future studies. As of anti-viral agents, aerosolized ribavirin therapy has been used for high-risk patients, but this formula is generally not available in Japan [15–18]. Moreover, ribavirin has shown poor efficacy when used as monotherapy. Some reports have suggested that ribavirin is effective in preventing the progression of LRTI when combined with high-titer immunoglobulin, palivizumab, or other treatment options during the URTI period. Further investigation is necessary since the number of patients reported in each study is small [15–18]. In our study, aerosolized ribavirin and intramuscular palivizumab were used after progression to LRTI in one patient (Patient #11), but unfortunately did not work. To summarize, there are no established effective treatment for RSV infections to date, and more effective anti-viral therapy for RSV is urgently required for these high-risk cases.

Because RSV only causes mild symptoms when infected in healthy individuals including families or health care providers, it is quite difficult to completely prevent RSV transmission to the patient. Therefore, it is important to immunize the patients themselves to protect them from RSV. Since August 2013, prophylactic administration of palivizumab has been expanded for use in patients younger than 2 years with immunodeficiency in Japan, including patients with malignancies [7]. It is expected that this expansion of palivizumab indication would effectively prevent severe RSV infection in Japanese patients with hematological malignancies, although its efficacy must be further evaluated. However, as many of the cases suffer from RSV infections before or during the initial induction course as shown in the present study, prophylactic palivizumab might not be in time for effective prevention if the patients are already exposed to RSV shortly before or at diagnosis. In that sense, universal vaccination of RSV, which is currently underway, would be more effective.

In conclusion, the prognosis of RSV disease in pediatric hematological malignancies was poor. Because the effective treatment strategy is not yet established, the effective prophylaxis and treatment strategies for severe RSV disease must be investigated.

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Compliance with ethical standards

Conflicts of interest The authors have no financial relationships or other conflicts of interest to disclose relevant to this article to disclose.

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