Original Article

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Acute Kidney Injury in Myeloid Leukemia of Down Syndrome: Risk Factors and Outcomes

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Abstract:

Objective: To identify the risk factors and describe the outcomes of patients who developed acute kidney injury (AKI) during treatment for myeloid leukemia of Down syndrome (ML-DS).

Material and Methods: The medical records of 23 Down syndrome patients under the age of 15 who had been diagnosed with acute myeloid leukemia (AML) and were being treated at a major tertiary care referral facility in Southern Thailand were reviewed. The identification of factors associated with AKI was done using logistic regression. The Kaplan-Meier method was used to calculate survival probabilities.

Results: Eight (34.8%) patients developed AKI during their course of chemotherapy with a median time from the first visit to the AKI event of 1.1 (IQR 0.7, 3.1) months. Higher levels of blast cells (OR: 1.19, 95% CI: 1.05-1.98) and septic shock during the course of chemotherapy (OR: 621.1, 95% CI: 2.40-Inf.) were independently associated with AKI. The 1-year overall survival rate was 26.1%. The median survival times among those who developed AKI and those who did not were 1.94 and 10.7 months, respectively

Conclusion: About one-third of the cases with ML-DS in our cohort developed AKI during the course of chemotherapy. The risk factors of AKI were higher peripheral blast count and septic shock during chemotherapy.

Keywords: acute kidney injury, childhood acute leukemia, down syndrome, myeloid leukemia of Down syndrome

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Introduction

Down syndrome (DS) has been associated with an increased risk of hematologic malignancy, particularly acute myeloid leukemia (AML).[1–3] Patients with myeloid leukemia of Down syndrome (ML-DS) have distinct characteristics such as aberrant chemotherapy metabolic clearance which leads to enhanced chemotherapeutic sensitivity and treatment response but also increased treatment-related toxicities.[4–7] One of the most common complications in patients with AML is acute kidney injury (AKI).[8] Previous studies of AKI in childhood AML reported 30-50% incidences of AKI and that age at diagnosis of more than 10 years, septic shock during their course of chemotherapy, and impaired kidney function before treatment were independent factors of AKI.[9,10] However, there are scarce data on AKI in ML-DS. In consideration of the limited data and uncertain risk factors, this study aimed to identify the risk factors and describe the outcomes in ML-DS patients who developed AKI during treatment for AML.

Material and Methods

We retrospectively reviewed the medical records of all children aged under 15 years diagnosed with AML from May 2003 to August 2019 at the Pediatric Oncology Division, Department of Pediatrics, Songklanagarind Hospital, a tertiary care referral center in Southern Thailand. We selected eligible cases with a Down syndrome diagnosis. The study was approved by the Human Research Ethics Committee of the institute. The clinical data included biological sex, age, initial laboratory examinations, chemotherapy, and complications such as infection. The treatment protocol was separated into three periods. From 2003 to 2008, the majority of patients received the Berlin-Frankfurt-Münster (BFM)-83 regimen.[11] Between 2008 and 2014, the patients were treated with the BFM-98 regimen[12], and after 2014, all patients were given chemotherapy following the Children's Oncology Group protocol.[13] All of our patients received reduced-dose chemotherapy as recommended by the Children's Oncology Group.[7,14,15] Laboratory tests for baseline values before induction chemotherapy were complete blood count, kidney function, electrolytes, calcium, phosphate, uric acid, lactate dehydrogenase (LDH), and liver function. These tests were performed weekly throughout their stay. Patients who had additional concerns, such as infection or AKI, had additional laboratory tests conducted as indicated. After the induction chemotherapy regimen, post-treatment responses were assessed. Overall survival was calculated using the time from the first diagnosis to death or the last follow-up.

AKI was defined as a rise in serum creatinine (SCr) of 0.3 mg/dL or 1.5-fold from baseline over 7 days from nadir to peak and higher than upper normal SCr for age, according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[16] The original Schwartz formula with a modified Jaffe assay[17] and the modified Schwartz formula with enzymatic creatinine findings[18] were used to calculate the estimated glomerular filtration rate (eGFR) to measure kidney function. An eGFR greater than 90 mL/min/1.73 m^2 was considered as normal. Tumor lysis syndrome was assessed according to the Cairo and Bishop criteria.[19] Septic shock was defined following the International Pediatric Sepsis Consensus Guidelines.[20]

Statistical analysis

For continuous variables, descriptive statistics were reported using the median and interquartile range (IQR). For comparison of categorical variables, the chi-square or Fisher's exact test was used, and for continuous variables, the rank-sum test was used. The initial multivariable logistic regression model for assessing independent factors contained variables with a p-value less than 0.1 from the univariate study. Using a stepwise backward elimination procedure based on the likelihood ratio test, the final model was chosen. The factors that predicted AKI are

shown as adjusted odds ratios (ORs) with 95% confidence interval (CI). Survival probabilities were calculated using the Kaplan–Meier method and plotted to compare the groups. A p-value less than 0.05 was considered significant.

Results

During the study period, 153 children were diagnosed with AML, and 26 of them had previously been diagnosed with DS. Of these, data on the 127 non-DS patients were reported separately.[10] Three of the 26 had incomplete data, resulting in a total of 23 individuals being included in the study. Twelve (52.2%) were boys, with a median age at diagnosis of 2 (IQR 1.6, 2.7) years. The demographic and clinical data of all subjects are shown in Table 1. Eight (34.8%) patients developed AKI during their course of chemotherapy, with a median time from the first visit to the AKI event of 1.1 (IQR 0.7, 3.1) months. The majority of AKI occurrences (7 of 8) were stage 2 AKI, the other was stage 1, and none received kidney replacement treatment.

Table 1 Comparison of demographic characteristics by development of acute kidney injury

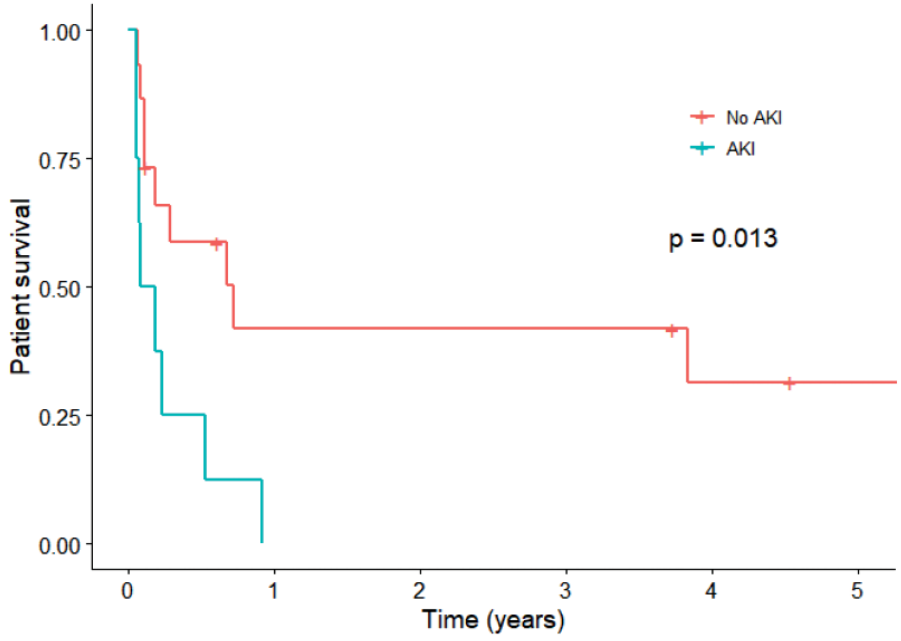
	AKI (n=8)	No AKI (n=15)	Total (n=23)	p-value
Male, n (%)	6 (75.0)	6 (40.0)	12 (52.2)	0.193
Age at diagnosis (years), median (IQR)	1.7 (1.4, 1.9)	2.3 (1.9, 3.1)	2.0 (1.6, 2.7)	0.114
BMI z-score, median (IQR)	0.5 (-1.3, 1.1)	-0.2 (-0.6, 0.7)	-0.1 (-0.9, 1.1)	0.821
Morphology, n (%)				1
AMKL	7 (87.5)	14 (93.3)	21 (91.3)	
Other	1 (12.5)	1 (6.7)	2 (8.7)	
Hemoglobin (g/dL), median (IQR)	7.6 (5.7, 8.5)	8.0 (5.2, 9.5)	8.0 (5.2, 9.3)	0.605
Hematocrit (%), median (IQR)	23.4 (17.4, 25.0)	24.0 (16.5, 28.1)	23.8 (16.5, 27.8)	0.651
WBCs (/uL), median (IQR)	32,350 (15,793, 67,650)	7,000 (4,330, 18,950)	13,370 (5,115, 44,600)	0.022
Peripheral blasts (%), median (IQR)	59.5 (47.8, 76.2)	10.0 (5.0, 21.5)	14.0 (6.5, 50.5)	0.002
Platelet count (/uL), median (IQR)	26,500 (16,750, 75,250)	27,000 (13,000, 41,000)	27,000 (13,000, 49,500)	0.723
BUN (mg/dL), median (IQR)	11.2 (7.9, 13.8)	12.9 (10.5, 20.2)	12.3 (8.9, 16.2)	0.333
Creatinine (mg/dL), median (IQR)	0.6 (0.4, 0.7)	0.4 (0.3, 0.5)	0.4 (0.3, 0.6)	0.155
eGFR (mL/min/1.73 m^2), median (IQR)	107.1 (73.6, 122.8)	105.4 (92.1, 117.9)	105.5 (81.3, 117.9)	0.974
Calcium (mg/dL), median (IQR)	9.0 (8.9, 9.1)	9.0 (8.9, 9.6)	9.0 (8.9, 9.2)	0.496
Phosphorus (mg/dL), median (IQR)	4.4 (3.5, 5.2)	4.6 (4.1, 5.0)	4.6 (4.0, 5.0)	0.674
Uric acid (mg/dL), median (IQR)	4.5 (3.7, 5.6)	5.6 (4.4, 7.3)	5.2 (3.8, 7.3)	0.232
ALP (IU/L), median (IQR)	126 (101, 160)	139 (115, 196)	139.0 (110, 180)	0.401
LDH (U/L), median (IQR)	2,705 (1,806, 4,963)	914 (815, 2,186)	2,095 (835, 3,774)	0.142
Albumin (g/dL), median (IQR)	3.8 (3.6, 4.0)	3.8 (3.5, 4.2)	3.8 (3.5, 4.2)	0.673
Tumor lysis syndrome, n (%)	1 (12.5)	1 (6.7)	2 (8.7)	1
Chemotherapy protocol, n (%)				0.114
BFM-83	7 (87.5)	6 (40.0)	13 (56.5)	
BFM-98	1 (12.5)	5 (33.3)	6 (26.1)	
COG	0 (0.0)	4 (26.7)	4 (17.4)	
Septic shock, n (%)	6 (75.0)	3 (20.0)	9 (39.1)	0.023

AKI=acute kidney injury, AMKL=acute megakaryoblastic leukemia, ALP=alkaline phosphatase, BFM=Berlin-Frankfurt-Münster, BMI=body mass index, BUN=blood urea nitrogen, COG=the Children's Oncology Group, eGFR=estimated glomerular filtration rate, LDH=lactate dehydrogenase, WBC=white blood cell

Table 1 shows the results of the univariate analysis to determine factors associated with AKI among the 8 patients who developed AKI and the 15 patients who did not. The patients who developed AKI had significantly higher WBC counts at diagnosis (32.4 vs 7.0×10^3/uL, p-value=0.022), higher peripheral blasts (59.5% vs 10.0%, p-value=0.002), and a greater proportion of septic shock (75.0% vs 20.0%, p-value=0.023) during their course of chemotherapy than those who did not develop AKI. Other clinical variables, including sex, age at diagnosis, body mass index z-score, SCr, eGFR, chemotherapy protocol, and tumor lysis syndrome, were not found to be associated with the development of AKI.

Eleven of the 13 (84.6%) patients achieved remission after induction chemotherapy. Three of the 11 patients subsequently relapsed at a median time of 3.7 (IQR 3.6, 13.3) months.

Seventeen patients died with the main cause of death being infection (n=12). The 1-year overall survival rate was 26.1%. Nine of the 12 with infection died from febrile neutropenia during their first induction chemotherapy while 3 entered remission after their induction chemotherapy but died during a later course. Two patients who did not enter remission died during re-induction chemotherapy. All 8 patients who had AKI died while 9 out of 15 without AKI died. The median survival times among those who developed AKI and those who did not were 1.9 and 10.7 months, respectively (Figure 1, p-value=0.013). In our study, the mean (S.D.) follow-up time was 2.3 (3.9) years.



AKI=acute kidney injury, p=p-value

Figure 1 Kaplan-Meier survival curve of study patients with myeloid leukemia of Down syndrome stratified by the development of acute kidney injury

Table 2 Logistic regression results identifying factors associated with acute kidney injury in the study childhood myeloid leukemia of Down syndrome patients

	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value†
Septic shock: yes vs no	12.0 (1.56-92.3)	621.1 (2.40-Inf.)	0.012
Peripheral blasts	1.09 (1.02-1.17)	1.19 (1.05-1.98)	<0.001

†likelihood-ratio test, CI=confidence interval, Inf.=infinite, OR=odds ratio

Multivariate analysis showed that the factors independently associated with AKI development were higher levels of blast cells (OR: 1.19, 95% CI: 1.05-1.98) and septic shock during the course of chemotherapy (OR: 621.1, 95% CI: 2.40-Inf.) (Table 2).

Discussion

Regarding the prevalence and risk factors of AKI in AML children, there are, to our knowledge, only three earlier reports of non-DS children with AML.[9,10,21] In one study, Du Plessis et al. found that 33.9% of the children with AML developed AKI during their first chemotherapy session, and that severe sepsis and an age at diagnosis of more than 10 years were independent predictors of AKI.[9] In another study, Fisher et al. found that AKI was associated with older age, black patients, and drug exposure duration of more than 48 hours for vancomycin or 10 days for carbapenem.[21] And an earlier report from our institution on non-DS childhood AML found 50.0% of 112 patients developed AKI during the AML treatment, with associated factors of age ≥10 years at diagnosis, impaired kidney function before treatment, and septic shock during the course of chemotherapy.[10] However, there is a scarcity of information about AKI in children with ML-DS. This is the only study that we are aware of that focuses on the prevalence, risk factors, and outcomes of AKI in children with ML-DS. In our study, a third of the children with ML-DS developed AKI. Septic shock during the course of chemotherapy and higher levels of peripheral blasts were found to be independent predictors of AKI in our patients. This could be explained by the fact that high WBCs and blast cells generally respond well to chemotherapy, leading to a greater burden from cell lysis, which can contribute to AKI.

Past studies have reported some similarities between DS and non-DS patients related to age at diagnosis. In non-DS patients, increasing age, especially more than 10 years old, was one of the poorest prognostic factors[22,23], while in DS patients, age at diagnosis greater than 4 years was associated with lower survival.[24,25] A large majority of our patients (91.2%) were under the age of 4 years. However, with our current knowledge and treatment, the prospects of survival for children with ML-DS remain poor. We found a much higher rate of infection and infection-related death among DS patients than in previous reports, resulting in a poorer prognosis when compared to other studies.

One of the factors associated with AKI in our study, which is consistent with other studies[9,10], was septic shock. In our study, septic shock was not only a risk related to AKI, but it was also the major cause of death. Previous studies found that septic shock was the most common complication and the leading cause of death in both DS and non-DS AML patients.[26-29] In an earlier study conducted from 1988 to 1995, Riley et al. found that 65.9% of 341 children with AML died from infection.[27] Dix et al. reported 77.1% mortality from infection in a study done from 1995 to 2004.[28] Craze

et al. reported a 55.0% mortality rate from sepsis and/or cardiomyopathy in 45 ML-DS children[26], and Abildgaard et al. reported infection was the most common cause of death (46.7%) in ML-DS patients in Nordic countries[29], results which are consistent with our findings. More than two-thirds of our patients died from infection and 43.5% (10 of 23) died from febrile neutropenia after induction chemotherapy. However, there was no information about AKI in any of the preceding studies.

Despite evidence that children with ML-DS have a better outcome when less aggressive chemotherapy regimens are used[30,31], the survival outcomes in our study were poor, particularly in those who developed AKI. Earlier studies describing the outcomes of DS patients reported overall survival rates for treated ML-DS patients of 70 and 90.0%, and 3-year survival rates of 91.0%.[25,26] A previous study from a resource-limited country found that the overall survival in patients with ML-DS was 57.1%.[32] However, overall survival was only 26.1% in our study, with no patients with AKI surviving. This finding was consistent with prior non-DS patient results in Thailand, a resource-limited country, where overall survival in one study was only 22.3%[10] and 5-year survival rates in 2 other studies were 22.1 and 35.1%.[33,34]

Herein we offer a pioneer study that focuses on the prevalence, risk factors, and outcomes of AKI in children with ML-DS. However, the study had some limitations. First, we had a small sample size due to the low prevalence of ML-DS. Second, the evaluation of AKI in this study was not fully comprehensive because information involving urine output was not available in the hospital records, an inherent problem in retrospective studies such as this one. Lastly, the study covered a 16-year period from 2003-2019, during which time the patients received different chemotherapy protocols and supportive treatment. This may have caused some degree of confounding in terms of separating independent factors for AKI.

Conclusion

About one-third of the patients with ML-DS in our cohort developed AKI during the course of chemotherapy. A higher peripheral blast count and septic shock during the course of chemotherapy were found to be associated factors of AKI. Despite dose adjustments of chemotherapy, our patients still had high rates of infection and mortality. Further studies are needed to identify optimal treatment protocols with the aim to reduce mortality rates and treatment-related toxicity.

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Conflict of interest

There are no relevant conflicts of interest for the authors to disclose.

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