Acute kidney injury and childhood acute myeloid leukemia

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Abstract

Background: Pediatric data on the epidemiology of acute kidney injury (AKI) in acute myeloid leukemia (AML) are limited, although the incidence of AKI appears to be very high in this patient group. The aim of this study was to assess the prevalence of and factors associated with AKI in childhood AML during chemotherapy treatment. Materials and methods: The medical records of 112 children aged under 15 years diagnosed with AML who received chemotherapy in a major tertiary care referral center in Southern Thailand were reviewed. Logistic regression was used to identify factors associated with AKI. Results: Fifty-six (50%) children had 69 AKI events. The median time from AML diagnosis to the first AKI was 29.5 days (interquartile range: 11.0-92.8). Age at diagnosis [?] 10 years (OR 2.75, 95% CI 1.09-6.93), glomerular filtration rate < 90 mL/min/1.73 m2 at AML diagnosis (OR 7.58, 95% CI 1.89-30.5) and septic shock (OR 22.0, 95% CI 4.63-104.3) were independently associated with AKI. Conclusions: Childhood AML has a high rate of renal injury with 50% having AKI. Age [?] 10 years at diagnosis, impaired renal function before treatment, and septic shock were strongly associated with AKI.

Introduction

Acute kidney injury (AKI) is one of the most common complications in children with cancer, including acute myeloid leukemia (AML). A study from Korea reported that among childhood cancer patients, AKI had the highest incidence in patients with AML (88.4%).[1] AKI can be a direct effect of the malignancy, a complication of the malignancy, a consequence or adverse effect of chemotherapy, and other medications such as antibiotics or diuretics.[2]Previous studies have reported that AKI was independently associated with increased mortality, ventilation requirement, hospital length of stay and daily costs.[3,4]

Childhood AML refers to a heterogeneous group of diseases classified according to morphology, lineage, and genetics.[5]Globally, AML represents 15%-20% of leukemias in children[6] and accounts for 27% of all leukemias in Southern Thailand.[7] The overall survival rates of children with AML have seen improvement over the past three decades, from 30-50% to the current 5-year survival rates ranging from 65% to 75%.[8,9] Its prognosis depends on age at diagnosis and type of AML, including a range of cytogenetic and molecular characteristics.

Among pediatric cancer patients, the 1-year cumulative incidence of AKI is highest in those with AML[1]; however, data on the epidemiology of AKI in children with AML are limited. A recent study reported a high incidence of AKI in pediatric AML (64%) with a strong association with age [?]10 years and severe sepsis; however, the sample size was only 58, which restricted the number of variables they could reliably analyze.[10] In this study we aimed to retrospectively assess the prevalence of and factors associated with AKI in childhood AML.

Materials and methods

We retrospectively reviewed the medical records of all children aged under 15 years and diagnosed with AML who received an AML chemotherapy protocol from May 2003 to August 2019 at the Pediatric Oncology Divi-

sion, Department of Pediatrics, Songklanagarind Hospital, the major tertiary care-referral center in Southern Thailand. The study was approved by the Human Research Ethics Committee of the institute. Clinical data including gender, age, tumour morphology, flow cytometry, treatment courses and laboratory investigations were collected. The treatment protocol was divided into 3 periods. From 2003-2008, most patients received chemotherapy consisting of the Berlin-Frankfurt-Münster (BFM)-83 regimen.[11] Between 2008 and 2014, the chemotherapy regimen involved 6 cycles of the BFM-98 regimen.[12] After 2014, all patients received chemotherapy according to the Children's Oncology Group.[13] All patients underwent similar laboratory investigation protocols for each session of chemotherapy treatment including renal function. Posttreatment responses were evaluated after patients completed the induction chemotherapy course. Overall survival was calculated from the date of the first diagnosis to date of death or last follow-up.

We defined AKI following the Kidney Disease: Improving Global Outcomes (KDIGO) criteria,[14] i.e. a rise in serum creatinine (SCr) [?] 0.3 mg/dL within 48 hours or 1.5-fold from baseline over 7 days from nadir to peak and higher than upper normal SCr for age. Severe AKI was defined as AKI stage 3 (SCr rise of at least 3-fold from baseline in 7 days). Estimated glomerular filtration rate (eGFR) was used to determine renal function by calculating creatinine clearance using the original Schwartz formula with a modified Jaffe assay[15] and modified Schwartz formula with enzymatic creatinine results (after May 2011).[16] An eGFR was considered normal if [?] 90 mL/min/1.73 m^2. Tumor lysis syndrome was diagnosed by the presence of two or more of the following abnormal conditions: hyperkalemia ([?] 6 mmol/L), hyperuricemia ([?] 8 mmol/L), hyperphosphatemia ([?] 6.5 mmol/L), and hypocalcemia (< 7 mmol/L) within 3 days before or 7 days after the initiation of chemotherapy according to the Cairo and Bishop criteria.[17] Septic shock was defined as per international pediatric sepsis consensus guidelines.[18]

Statistical analysis

Statistical analysis was performed using R version 4.1.0. Demographic data are presented as frequency with percentage, means and standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate. Categorical data were compared using the Chi-square test or Fisher's exact test, as appropriate. Student's t-test or the Mann-Whitney U test were used for comparison of continuous data between patients who had or did not have AKI, as appropriate. Multivariate logistic regression was used to identify factors independently associated with AKI. Survival probabilities were calculated using the Kaplan-Meier method and plotted to compare the groups. Statistical tests were considered significant at a P value < 0.05.

Results

A total of 127 children were diagnosed with AML during the study period. Of these, 15 were excluded: 9 had incomplete data and 6 were diagnosed with AKI from other hospitals and exposed to nephrotoxic medications prior to being referred to our hospital. Of the 112 patients included in the study, 71 were boys (63.4%) and their mean (SD) age was 7.1 (4.1) years. Baseline demographic and clinical data are presented in Table 1.

Prevalence of AKI

During their chemotherapy treatment, 56 patients (50%) developed AKI and 13 had a second AKI episode for a total of 69 AKI events during the study period. Fifteen severe AKI episodes developed in 13 patients (21.7%). The median time from the first visit to the first AKI and median follow up time were 29.5 days (IQR 11-93) and 10.9 months (IQR 3.6-31.1), respectively. Figure 1 shows the maximum creatinine levels in all AKI patients stratified by severity of AKI and age at diagnosis.

Factors associated with AKI

Table 1 compares demographic characteristics stratified by development of AKI. In the group of patients who had at least 1 episode of AKI, the mean age at diagnosis was significantly higher (8.5 vs 5.7 years, P = 0.002), and the proportions with impaired initial eGFR < 90 mL/min/1.73 m^2 (21.4% vs 5.4%, P = 0.026) and septic shock (35.7% vs 3.6%, P < 0.05) were significantly higher compared to the group who did not

develop AKI. Six patients (5.4%) were diagnosed with tumor lysis syndrome at the initial AML diagnosis and all of them developed AKI during their first admission. The median time from the first visit to the first AKI episode was 12.5 days (IQR 2.8-20.8). The association between AKI and chemotherapy protocol was not significant; however, AKI occurred more frequently among those treated with the BFM-83 protocol than the other two protocols while patients receiving the Children's Oncology Group regimen had the lowest proportion of AKI incidents.

On multivariate analysis, septic shock was the most important risk factor of AKI, followed by impaired renal function before initiation of chemotherapy and age at diagnosis [?] 10 years (Table 2).

Outcomes

Table 3 compares treatment outcomes between patients who developed AKI and those who did not. Renal replacement therapy was performed in 3 patients (20% of the severe AKI patients). After the first cycle of chemotherapy, 77 patients (68.8%) had complete bone marrow remission. The proportion of patients with remission was significantly lower in the AKI group than in the non-AKI group (58.9% vs 78.6%, P = 0.041); however, there were no significant differences in the survival rates (Figure 2). Overall, there were 87 (77.7%) deaths in our cohort and the median survival time was 8.4 months (IQR 3.8-19.9).

Discussion

Our study found that half of our childhood AML patients developed acute kidney injury during their course of chemotherapy. AKI most commonly occurs in the early stages after the beginning of treatment, with a median time to first episode within one month of treatment initiation. Age at diagnosis [?] 10 years, impaired renal function at AML diagnosis, and septic shock were independent risk factors for AKI.

Pediatric data on the epidemiology of AKI in AML are limited, to our knowledge, to only two previous reports.[10,19] In one study, the incidence of acute renal failure was found to be 16.2%[19]; however, since acute renal failure does not include severe cases of AKI, the incidence of AKI may have been underreported. The high incidence of AKI found in our study is consistent with a study by Du Plessis et al, who also used the KDIGO criteria for defining AKI.[10]

In studies in both adulthood and childhood AML, one of the common findings was that older age (more than 10 years in children and more than 55-60 years in adults) was a significant independent risk factor for AKI.[10,19–21] These results correlated with the finding of other studies which found that the prognosis of AML gets worse with increasing age.[22,23]

We also found impaired initial renal function was strongly associated with a higher likelihood of one or more AKI incidents during admission in our study, consistent with a previous report in pediatric cancer patients from Korea.[1] We found 15 AML patients with impaired initial eGFR at their first AML diagnosis, 12 of whom developed at least 1 episode of AKI. There were no significant differences in white blood cell counts or occurrence of tumor lysis syndrome that may have contributed to kidney damage between patients with impaired eGFR and patients with normal initial renal function. None of the patients in our study had had previous investigations for preexisting renal tract anomalies, so we did not know the exact cause of impaired renal function in these patients. However, due to the high risk of developing AKI in impaired renal function patients, nephrotoxic medications should only be prescribed with caution and renal function should be closely monitored during treatment in these patients.

Regarding infections, the most common treatment-related toxicity and main cause of death was sepsis, which has been commonly associated with AKI in both noncancer and cancer patients.[8,24–26] Our study confirmed a strong association between septic shock and AKI during the course of chemotherapy, consistent with a previous pediatric AML study.[10] In terms of overall treatment outcomes in our study, the proportion of patients entering remission was significantly lower in the AKI group. This finding might be explained by a dose adjustment of chemotherapy in patients who developed AKI. However, there were no differences in either relapse or mortality rates between the two groups. As the only known effective regimens for treating childhood AML involve aggressive treatment, lowering the intensity of chemotherapy may be beneficial in

some patients, as this should lead to a decrease in associated infections and subsequent organ dysfunction, including AKI, and hopefully lead to decreased mortality, which is often related to organ-failure caused by sepsis rather than AML itself.

In conclusion, half of our childhood AML patients developed AKI during their chemotherapy treatment. Age [?] 10 years at diagnosis, impaired renal function before treatment, and septic shock were independent risk factors for developing AKI.

Conflict of Interest Disclosure: The authors have no conflicts of interest relevant to this article to disclose.

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Ethics statement

Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand.

Authorship contributions

All authors made significant contributions to both the research and the writing of the manuscript and have read and approved the final manuscript.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

References

1. Park PG, Hong CR, Kang E, et al. Acute kidney injury in pediatric cancer patients. J Pediatr 2019;208:243–250.

2. Luciano RL, Brewster UC. Kidney involvement in leukemia and lymphoma. Adv Chronic Kidney Dis 2014;21:27–35.

3. Bharat A, Mehta A, Tiwari HC, Sharma B, Singh A, Singh V. Spectrum and immediate outcome of acute kidney injury in a pediatric intensive care unit: a Snapshot Study from Indian Subcontinent. Indian J Crit Care Med 2019;23:352–355.

4. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med 2017;376:11–20.

5. Rubnitz JE. How I treat pediatric acute myeloid leukemia. Blood 2012;119:5980–5988.

6. Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. Int J Cancer 1988;42:511–520.

7. Demanelis K, Sriplung H, Meza R, et al. Differences in childhood leukemia incidence and survival between Southern Thailand and the United States: a population-based analysis. Pediatr Blood Cancer 2015;62:1790–1798.

8. Rasche M, Zimmermann M, Borschel L, et al. Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. Leukemia 2018;32:2167–2177.

9. Rubnitz JE, Inaba H, Dahl G, et al. Minimal residual disease-directed therapy for childhood acute myeloid leukaemia: results of the AML02 multicentre trial. Lancet Oncol 2010;11:543–552.

10. Du Plessis L, Rassekh SR, Mammen C. High incidence of acute kidney injury during chemotherapy for childhood acute myeloid leukemia. Pediatr Blood Cancer 2018;65:e26915.

11. Creutzig U, Ritter J, Schellong G. Identification of two risk groups in childhood acute myelogenous leukemia after therapy intensification in study AML-BFM-83 as compared with study AML-BFM-78. AML-BFM Study Group. Blood 1990;75:1932–1940.

12. Creutzig U, Zimmermann M, Lehrnbecher T, et al. Less toxicity by optimizing chemotherapy, but not by addition of granulocyte colony-stimulating factor in children and adolescents with acute myeloid leukemia: results of AML-BFM 98. J Clin Oncol 2006;24:4499–4506.

13. Cooper TM, Franklin J, Gerbing RB, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: a report from the Children's Oncology Group. Cancer 2012;118:761–769.

14. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1–138.

15. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am 1987;34:571–590.

16. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol 2009;4:1832–1843.

17. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3–11.

18. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.

19. Fisher BT, Zaoutis TE, Leckerman KH, Localio R, Aplenc R. Risk factors for renal failure in pediatric patients with acute myeloid leukemia: a retrospective cohort study. Pediatr Blood Cancer 2010;55:655–661.

20. Lahoti A, Kantarjian H, Salahudeen AK, et al. Predictors and outcome of acute kidney injury in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. Cancer 2010;116:4063–4068.

21. Ballo O, Eladly F, Buttner S, et al. Acute kidney injury adversely affects the clinical course of acute myeloid leukemia patients undergoing induction chemotherapy. Ann Hematol 2021;100:1159–1167.

22. Creutzig U, Buchner T, Sauerland MC, et al. Significance of age in acute myeloid leukemia patients younger than 30 years. Cancer 2008;112:562–571.

23. Rubnitz JE, Pounds S, Cao X, et al. Treatment outcome in older patients with childhood acute myeloid leukemia. Cancer 2012;118:6253–6259.

24. Dix D, Cellot S, Price V, et al. Association between corticosteroids and infection, sepsis, and infectious death in pediatric acute myeloid leukemia (AML): results from the Canadian Infections in AML Research Group. Clin Infect Dis 2012;55:1608–1614.

25. Riley LC, Hann IM, Wheatley K, Stevens RF. Treatment-related deaths during induction and first remission of acute myeloid leukaemia in children treated on the Tenth Medical Research Council acute myeloid leukaemia trial (MRC AML10). The MCR Childhood Leukaemia Working Party. Br J Haematol 1999;106:436–444.

26. Vachvanichsanong P, Dissaneewate P, Lim A, McNeil E. Childhood acute renal failure: 22-year experience in a university hospital in Southern Thailand. Pediatrics 2006;118:e786–791.

TABLE 1 Comparison of demographic characteristics by development of AKI

TABLE 2 Logistic regression results for identifying factors associated with AKI in childhood AML patients

TABLE 3 Comparison of treatment outcomes by development of AKI

FIGURE 1 Median (interquartile range) of maximum creatinine levels in 56 childhood AML patients with AKI stratified by AKI severity and age at diagnosis

FIGURE 2 Kaplan-Meier survival curve of the 112 study patients with AML stratified by development of AKI

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