Pediatric Acute Myeloid Leukemia and Hyperleukocytosis with WBC count greater than 50×10^9/L

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November 10, 2020

Abstract

Background: Acute myeloid leukemia (AML) and hyperleukocytosis are related to an unfavorable prognosis. The impact of hyperleukocytosis on the prognosis of pediatric AML has not been fully explained so far. We aimed to assess the clinical characteristics and prognosis of pediatric AML with hyperleukocytosis, referred to as white blood cell (WBC) count [?]50×10^9/L. Methods: A total of 307 newly diagnosed non-acute promyelocytic leukemia patients were continuously enrolled at our center from October 2005 to September 2015. 81 patients with initial leukocyte counts [?]50x10^9/L. The baseline demographic and clinical characteristics of AML patients were compared. Progression-free survival (PFS) and overall survival (OS) were documented. Results: Hyperleukocytosis occurred in 26.38% of AML patients, and FAB M5 subtype (n=41, 50.62%) and *FLT3-ITD* mutations (n=16, 19.75%) had a high proportion in AML and hyperleukocytosis. Overall mortality was significantly higher in patients with hyperleukocytosis than patients without hyperleukocytosis (50.62% vs. 35.84%, P=.020). Patients with hyperleukocytosis had a lower 10-year PFS and OS rates than those without hyperleukocytosis (44.4%+-9.4% vs. 59.7%+-5.5%, P=.041; 49.4%+-9.4% vs. 64.2%+-5.4%, P=.051, respectively). There were similar PFS and OS rates between the subgroups of patients with WBC count 50-100x10^9/L and WBC count [?]100x10^9/L (43.8%+-13.3% vs. 44.9%+-12.3%, P=.507; 46.9%+-13.3% vs. 51.0%+-12.3%, P=.907, respectively). In all patients with hyperleukocytosis, male and FAB M5 subtype patients had a significantly inferior survival, while CBF-AML had a better survival. Conclusions: A WBC count greater than 50x10^9/L at onset was a critical predictive adverse factor in pediatric AML.

Introduction

Acute myeloid leukemia (AML) is a clinical and genetic heterogeneous disease that accounts for 15–20% of all childhood leukemias.[1] Accurate diagnosis and treatment strategies have resulted in tremendous improvements in the overall survival (OS) rate of pediatric AML, which is now nearly 60%.[2-5] Different subtypes of AML vary in clinical presentation characteristics and therapeutic effects. AML and hyperleukocytosis have been associated with an unfavorable prognosis,[6,7] which can lead to a higher probability of early death due to complications of leukostasis, tumor lysis syndrome, and disseminated intravascular coagulation (DIC) .[8]

Hyperleukocytosis has no explicit diagnostic criteria so far, but usually refers to white blood cell (WBC) counts greater than 100×10^9/L in the peripheral blood of patients with acute leukemia.[9] However, it should be noted that WBC counts below this arbitrary threshold can also cause leukocytosis-related complications. Hyperleukocytosis has been defined as more than 50×10^9/L in some studies in adults with AML.[10-12]To our knowledge, no study has reported the characteristics and prognosis of hyperleukocytosis (described as WBC

count [?]50x10^9/L) in pediatric AML patients. The objective of our study was to contribute to recognizing this group of pediatric AML. In this study, we analyzed the clinical characteristics (sex, age, cytogenetics, molecular biology) and outcome in an unselected cohort of de novo non-M3 AML pediatric patients.

Methods

Patients and methods

We retrospectively studied 307 newly diagnosed non-M3 AML patients at our center over ten years from October 2005 to September 2015. The follow-up period ranged from 1 to 176 months, with a median follow-up time of 35 months. AML patients [?]15 years old were consecutively enrolled, and acute promyelocytic leukemia patients were excluded. The diagnosis and morphologic subtype of AML was based on the French-American-British (FAB) classification.[13] All patients were classified into two groups according to the WBC count at diagnosis: those without hyperleukocytosis (WBC count <50x10^9/L group) versus those with hyperleukocytosis (WBC count [?]50x10^9/L group). Moreover, patients in the hyperleukocytosis group were divided into two subgroups: 32 patients with WBC count 50-100x10^9/L and 49 with WBC count [?]100x10^9/L. Cytogenetic risk category accorded to 2017 European leukemia net(ELN) .[14]

Chemotherapyregimen

All patient in this study received Chinese Academy of Medical Science (CAMS)-2009 regimen, referred to the AML99 program for chemotherapy.[15] The standard induction treatment regimen consisted of etoposide,150 mg/$m^2$with a 2-hour infusion on days 1-5, 3 days of idarubicin ,8 mg/m^2 iv on days 6-8, and seven days of cytarabine, 200 mg/m^2 on days 6-12. A second course of induction therapy was given if not achieved CR. The five courses of consolidation treatment consisted of high-dose cytarabine combined with etoposide or idarubicin.[16] Patients with high risk or secondary remission after recurrence recommended to receive allogeneic hematopoietic stem cell transplantation(HSCT). If there was no condition to perform HSCT, consolidation and strengthen treatment should be continued. The patients received prophylactic treatment for central nervous system through intrathecal multi-drug chemotherapy at once per course of treatment.

Statistical analysis

Progression-free survival (PFS) and OS were the primary endpoints of the study. PFS referred to the time from the beginning of treatment to disease progression or death. OS was defined as the time of death due to any cause. Categorical variables are expressed as total numbers and percentages. Because the continuous variables are not normally distributed, median, minimum and maximum values were used as descriptive statistics. Clinical characteristics, complete remission (CR) rate, and mortality rate-related variables were compared. Categorical variables were compared using χ^2 test, likelihood ratio χ^2 or Fisher's exact test, and differences in continuous variable were compared using nonparametric Mann–Whitney U-test. For the logistic proportional hazard regression models, the results were expressed as odds ratios (ORs), 95% confidence intervals (CIs) and P -values. Variables with P <.10 in univariate analysis were included in this model for multivariate analysis.P <.05 indicated statistical significance. The PFS and OS rates were estimated by Kaplan-Meier survival analysis, and the log-rank test was used for survival comparison. All tests were 2-sided. SPSS 25 was used for all statistical analyses.

Ethics approval

The Ethics committee of our institution approved the study.

Results

Demographics and clinical characteristics

We examined data on 307 pediatric AML patients between 2005 and 2015 and 81 patients (26.38%) with hyperleukocytosis. According to the WBC count, the baseline demographic and clinical characteristics of AML patients with and without hyperleukocytosis compared in Table 1. The proportion of males in the two groups was 55.31% and 61.73, respectively. Hyperleukocytosis at onset was high in patients with

the M5 subtype (n=41, 50.62%) in the FAB classification, whereas without hyperleukocytosis was high in patients with FAB M2 subtype (n=126, 55.75%). The proportion of intermediate cytogenetics and FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) was higher in patients with hyperleukocytosis than without hyperleukocytosis (54.32% vs. 32.30%, P<0.001; 19.75% vs. 3.98%, P <0.001). The proportion of favorable cytogenetics and core binding factor acute myeloid leukemia (CBF-AML) was lower in patients with hyperleukocytosis than without hyperleukocytosis (18.52% vs. 44.69%, P<0.001; 22.22% vs. 48.23%,P <0.001) (Table 1). The baseline demographic and clinical characteristics of hyperleukocytosis subgroups compared in Table 1S.

Impact of hyperleukocytosis on treatment response

Overall mortality was significantly higher in patients with hyperleukocytosis than in patients without hyperleukocytosis (50.62% vs. 35.84%,P =.020), while the CR rate after induction was similar between the two groups (75.31% vs. 76.99%,P =.759) (Table 2). Table 2S illustrates that the CR rate was significantly higher in favorable/intermediate cytogenetics in the WBC count 50-100$\times10^9$/L subgroup than the WBC count [?]100x10^9/L subgroup (92.31% vs. 63.64%,P =.013), and yet CR rate was no significant difference between the two subgroups in other circumstances. To our surprise, there was no significant difference in mortality rate between the two subgroups regardless of sex, age, cytogenetics or specific molecular alterations.

Correlation between clinical variables and hyperleukocytosis

According to the results of the multivariate logistic analysis, FAB M5 subtype and FLT3-ITD mutations had a high probability of developing hyperleukocytosis in childhood AML patients (P <0.001 and P =.001). At the same time, CBF-AML had a low probability of developing hyperleukocytosis in childhood AML patients (P =.020) (Table 3).

Impact of hyperleukocytosis on long-term outcomes

Figure 1A indicates that patients with hyperleukocytosis had a significantly lower 10-year PFS rate than patients without the hyperleukocytosis (44.4%+-9.4% vs. 59.7%+-5.5%, P =.041). Patients with hyperleukocytosis also had an inferior 10-year OS rate (49.4%+-9.4% vs. 64.2%+-5.4%, P =.051; Fig 1B), albeit this did not reach statistical significance. Further analysis showed similar 10-year PFS and OS rates (43.8%+-13.3% vs. 44.9%+-12.3%, P =.507; 46.9%+-13.3% vs. 51.0%+-12.3%,P =.907, respectively; Fig 1C and 1D) between the WBC count 50-100x10^9/L and WBC count [?]100x10^9/L subgroups.

Among patients with AML and hyperleukocytosis, male patients had a significantly lower 10-year PFS and OS rate than female patients (36.0%+-10.4% vs. 58.1%+-15.0%, P =.049; 40.0%+-10.6% vs. 64.5%+-14.5%,P =.023, respectively), and FAB M5 subtype had a significantly lower 10-year PFS and OS rate than another (34.1%+-12.6% vs. 55.0%+-12.1%, P =.017; 39.0%+-13.0% vs. 60.0%+-11.9%, P =.019, respectively). AML and hyperleukocytosis with*FLT3-ITD*had similar 10-year PFS and OS rate to without *FLT3-ITD*(43.8%+-18.1% vs. 44.6%+-10.4%, P =.490; 56.3%+-18.3% vs. 47.7%+-10.4%, P =.845, respectively).However,CBF-AML with hyperleukocytosis had a significantly higher 10-year PFS and OS rate than other hyperleukocytosis in pediatric AML (66.7%+-16.7% vs. 38.1%+-10.4%,P =.023; 72.2%+-15.8% vs. 42.9%+-10.6%, P =.028, respectively).

Discussion

Pediatric AML patients with hyperleukocytosis, usually refers to WBC counts greater than 100x10^9/L, have been reported to have a more dismal prognosis than patients without hyperleukocytosis.[6-8] However, WBC counts below 100x10^9/L can also cause leukocytosis-related complications and affect prognosis. Hyperleukocytosis has been defined as more than 50x10^9/L in some studies in adults with AML.[10-12] Hyperleukocytosis has had no definitive criteria heretofore. To the best of our knowledge, this study was the first report the characteristics and prognosis of hyperleukocytosis (described as WBC count [?]50x10^9/L) in pediatric AML patients. Moreover, this study was performed to further compare the clinical characteristics and prognoses of childhood AML patients with hyperleukocytosis with WBC count 50-100x10^9/L and those with WBC count [?]100x10^9/L in a single institution.

In this study, we defined a WBC count greater than $50x10^9$/L as the cut point for hyperleukocytosis. The incidence of hyperleukocytosis in childhood AML patients at diagnosis was 26.38% in our center, which is similar to published data .[10-12] In this study, patients with and without hyperleukocytosis had similar CR rates, and yet patients with hyperleukocytosis had a higher mortality rate than those without hyperleukocytosis. We further confirmed that the 10-year PFS and OS rates (P =.041, P =.051) between groups separated with this cutoff were significantly different at our institution. PFS and OS were similar within the subgroups. This fact indicates that a high leukocyte count (WBC count [?] $50x10^9$/L) is a significant marker of poor prognosis. Tien et al. observed that WBC counts significantly affected OS and pointed out that hyperleukocytosis was an independent poor prognostic factor.[11] Genetic characteristics and clinical treatment response as risk stratifications changed the clinical prognosis. Hence, WBC count [?] $50x10^9$/L should be classified as one of the risk stratification factors for pediatric AML.

Patients with AML-M5 often present with hyperleukocytosis, and patients with AML-M5 may experience serious symptoms of hyperleukocytosis.[17]In this study, half of patients had the FAB M5 subtypes in patients with AML and hyperleukocytosis. In all patients with hyperleukocytosis, FAB M5 subtype patients had a significantly inferior survival. Monocytic leukemia cells have more large-volume active lysosomes.[18]During chemotherapy, leukemia cells destroy and release a large number of lysosomes, which caused coagulopathy, metabolic disturbance, and even DIC and tumor lysis syndrome. It may be the main reason for the high mortality of M5 with hyperleukocytosis.[19]This may be one of the reasons for the increased mortality of children with AML and hyperleukocytosis.

Moreover, Male predominance was noted in a multicentric study in Brazil,[20] which was consistent with our data. In accord with our findings, pediatric AML and hyperleukocytosis were more males, who had significantly poorer 10-year PFS and OS rates than females. More than half of the AML-M5 patients experienced testicular relapse without previous systemic relapse.[21] Poor prognosis may be related to predominant acute monoblastic leukemia, extramedullary infiltration, and the blood-testis barrier as a refuge for leukemia cells. All of the above factors may lead to unsatisfactory chemotherapy effects, relapse and high mortality in male pediatric AML patients with hyperleukocytosis.

AML with*RUNX1-RUNX1T1((AML1/ETO)*or core-binding factor subunit beta- myosin heavy chain 11*(ΒΦβ-ΜΨΗ11)* has been considered a unique entity, which is collectively referred to as CBF-AML.[22]Most treatment protocols classify all children with CBF-AML as having a low-risk disease.[5] However, CBF-AML has a very high degree of clinical and biological heterogeneity.[23] WBC count, platelet count and cytogenetic were significant prognostic variables in CBF-AML.[24] In our study, CBF-AML had a low proportion of hyperleukocytosis in childhood AML patients. Moreover, hyperleukocytosis with CBF-AML had a significantly higher PFS and OS rate than hyperleukocytosis without CBF-AML. This statistical difference may also be due to relatively small sample size. More sample or experiments are needed to further confirm these findings.

The incidence of *FLT3-ITD* was 8.14% (25 out of 307 patients) in non-M3 pediatric AML in our study, which was consistent with previous reports.[25] Our data suggested that the incidence of*FLT3-ITD*mutations (n=16, 19.75%) was higher in AML patients with hyperleukocytosis than without hyperleukocytosis, and *FLT3-ITD* mutations had a high probability of developing hyperleukocytosis in childhood AML patients. These features were unanimous in WBC count above 100×10^9/L AML patients in the previous study.[8] The conformational changes in the juxtamembrane domain of the *FLT3* receptor caused by ITD mutations activate*FLT3-ITD*receptor tyrosine kinases, which causes proliferation, inhibits apoptosis and suppresses differentiation.[26,27] This may be the cause of leukocytosis in *FLT3-ITD* patients. In addition, *FLT3-ITD* mutation was an independent risk factor for poor outcome in pediatric acute myeloid leukemia.[28]Therefore, It was expected to improve the long-term survival of these patients by promising FLT inhibitors, Midostaurin and Sorafenib, combined with sequential chemotherapy or as maintenance after HSCT.[29]

In conclusion, more than 20% of AML patients have a WBC count greater than 50×10^9/L, which is defined as hyperleukocytosis in our study. Poor prognosis in terms of 10-year PFS and OS rates indicated that hyperleukocytosis was a critical predictive adverse factor in pediatric AML. In all patients with hyperleukocytosis, male and FAB M5 subtype patients had a significantly inferior survival, and the prognosis of CBF-AML

with hyperleukocytosis was good. To exploit more accurate treatment strategies, a more extensive range of WBC counts is needed to define hyperleukocytosis for stratify risk in children with AML.

Declarations

Funding This work was supported by The Special Fund for Education and Scientific Research of Fujian Provincial Department of Finance (2019-926) and The National Key Research and Development Program of China (2016YFC0901503).

Conflicts of interest None declared.

Ethics approval The Ethics committee of the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College approved the study (CAMS-2005/CAMS-2009, NCT03165851).

Consent for participate Parental/guardian of all patient consent for participate.

Consentfor publication Parental/guardian of all patient consent for publication.

Availability of data and materialthe raw data were uploaded as a supplementary material.

Author's contributions ALZ and LPL conceived and designed the study. ALZ and LPL drafted the initial manuscript and analyzed the data. MR, XYC, and CL reviewed the initial manuscript. CYW and YCZ supervised the work. LXC, XJC, WYY, YG, LZ, YZ, and YMC collected and provided patient clinical data. XFZ and MR assigned the protocol, and critically revised the manuscript for relevant intellectual content. All authors approved the final submitted version of the paper.

Acknowledgements All authors express thanks to Dr Meihui Yi, Yang Lan, Luyang Zhang, Yuli Cai, Jing Feng, Wenqi Wu. We want to acknowledge patients and their families for participating in the follow-up.

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Figure 1 . Kaplan–Meier analyses for PFS and OS rates of AML patients. Patients with hyperleukocytosis had a lower 10-year PFS and OS rates than those without hyperleukocytosis (P =.041 and P =.051; 1A, 1B). There was a similar 10-year PFS and OS rates between patients in the WBC count 50-100$\times 10^9$/L and WBC count [?]100x10^9/L subgroups (P =.507 and P =.907; 1C, 1D).

Supporting information

Additional supporting information may be found online in the Supporting Information section.

Table 1S. Clinical characteristic in subgroup of AML patients with hyperleukocytosis.

Table 2S. Complete remission and mortality rates in subgroup of AML patients with hyperleukocytosis.

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