Observational Study

Medicine®

OPEN

The prognostic value of the peripheral blood cell counts changes during induction chemotherapy in Chinese patients with adult acute myeloid leukemia

Yuan-Mao Huang, MD, PhD[a,b,c], Yan-Ni Wang, MD[a,b], Yi Zheng, MD[a], Li-Li Pan, MD[b], Yang Li, MD[b], Jing-Gang Li, MD, PhD[b], Shao-Yuan Wang, MD[a,b,*]

Abstract

To investigate the prognostic value of the circulating peripheral blood cell counts changes in acute myeloid leukemia (AML) at different time points during induction chemotherapy.

We retrospectively analyzed the clinical and laboratory data of 237 newly diagnosed AML patients admitted to Fujian Medical University Union Hospital from January 2011 to December 2014.

1. When primitive cells were first removed from the circulating peripheral blood, it was called peripheral blood blast clearance (PBBC). These patients were divided into two groups, according to PBBC. Statistical analysis showed that the day 5 of induction chemotherapy was a better cut-off for PBBC. PBBC$\leq$5 days is defined as early-blast-clearance, while PBBC $>$6 days is delayed-blast-clearance. There was significant difference between the two groups on complete remission (CR) rate (P = .002), recurrence-free survival (RFS) (P = .026) and overall survival (OS) (P = .001). 2. Multivariate analysis suggested PBBC is an independent prognostic factor for CR, RFS, and OS in AML. Receiver operating characteristic(ROC) curve analysis showed the CR rate of patients with white blood cell count less than 1.25×10^9/L was significantly higher than that of patients with white blood cell count more than 1.25×10^9/L ($P < .001$) at day 5 of induction chemotherapy, but the RFS and OS was no significantly different ($P > .05$).

The dynamics of peripheral blood blast in AML after initiation of induction chemotherapy, especially the time length to achieve PBBC, has important prognostic value for CR rate, RFS, and OS in AML patients. It is a simple and feasible method to evaluate the efficacy of AML.

Abbreviations: AML = acute myeloid leukemia, CR = complete remission, DBC = delayed-blast-clearance, EBC = early-blast-clearance, OS = overall survival, PBBC = peripheral blood blast clearance, RFS = recurrence-free survival, ROC = receiver operating characteristic, WBC = white blood cell count, WHO = World Health Organization.

Keywords: acute myeloid leukemia, overall survival, peripheral blood blast clearance, prognosis, recurrence-free survival

Editor: Kartik Anand.

YMH and YNW authors contributed equally to this work.

This work was supported by the National Natural Science Foundation of China (81470008, 81270609, 30770909, and 81770163), Fujian Province Health Education Joint Research Project (WKJ-2016-2-07), Special Funding of Fujian Provincial Department of Finance (2017-655), the Major Science and Technology Project of Fujian Province (2003F003, 2012Y4012, and 2019Y91010026), the Major Science and Technology Project of Fujian Medical University (09ZD008), the Natural Science Foundation of Fujian Province (2016J05209 and 2020J01122219), Youth Research Project of Fujian Provincial Health and Family Planning Commission (2016-2-47) and the Chinese National Clinical Key Subject Construction Project.

The authors thank Professor Xu Lin (Department of Pathology, Fujian Medical University Fuzhou, Fujian Province) for expert assistance with the data analysis.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Union Clinical Medical College, Fujian Medical University, [b] Department of Hematology, Fujian Institute of Hematology, Fujian Provincial Key Laboratory on Hematology, Fujian Medical University Union Hospital, Fuzhou, [c] Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou 363000, Fujian, P.R. China.

[*] Correspondence: Shao-Yuan Wang, Department of Hematology, Fujian Institute of Hematology, Fujian Medical University Union Hospital, Fuzhou 350001, P.R. China (e-mail: shaoyuanwang@mail.fjmu.edu.cn).

How to cite this article: Huang YM, Wang YN, Zheng Y, Pan LL, Li Y, Li JG, Wang SY. The prognostic value of the peripheral blood cell counts changes during induction chemotherapy in Chinese patients with adult acute myeloid leukemia. Medicine 2021;100:8(e24614).

Received: 17 May 2020 / Received in final form: 8 December 2020 / Accepted: 7 January 2021

http://dx.doi.org/10.1097/MD.0000000000024614

1. Introduction

The annual incidence of acute myeloid leukemia (AML) is 1.62/100,000, accounting for about 60% to 70% of adult acute leukemia, and the incidence is increasing year by year.[1] In recent years, the diagnosis and treatment of AML have been improved. The complete remission (CR) rate and overall survival (OS) also have been significantly improved recently.[2] Nevertheless, the recurrence-free survival (RFS) and long-term survival are still unsatisfactory due to the disease's clinical and genetic heterogeneity. 50% -70% of patients relapse after 3 years of CR.[3] The prognosis of AML is impacted by many factors,[4] including pre-treatment and post-treatment factors. In the early stages of diagnosis and treatment of AML, accurate clinical prognostic analysis, and more precise individualized treatment will reduce relapse and improve OS. In clinical practice, changes in peripheral blood cell counts in patients with AML after induction chemotherapy usually imply the *in vivo* chemosensitivity and toxicity. So whether peripheral blood changes after induction of AML can directly predict the therapeutic effect of the chemotherapy is worthwhile to study further. This study attempts to uncover the response of AML patients to induction chemotherapy by detecting the changes of peripheral blood cell counts in the first course of induction chemotherapy, to directly predict the therapeutic effect of AML patients by peripheral blood cell counts change, and to provide a feasible and straightforward parameter for clinical prognostic evaluation of AML.

Table 1

The clinical parameters of 237 AML patients at the time of initial diagnosis.

Age, yr	40.8 (15–77)
Gender	
Male	130/237
Female	107/237
AML subtype	
M0	8
M1	11
M2	80
M4	7
M5	119
M6	12
Cytogenetics subgroup	209
Favorable	20
Intermediate	173
Adverse	16
WBC count (10^9/L)	17.4 (0.5–447.06)
The proportion of neutrophils (%)	23.8 (0.57–94.9)
Proportion of mononuclear cells (%)	10.0 (0.7–82.7)
The proportion of lymphocytes (%)	25.0 (1.0–96.9)
Platelet count (109/L)	44.56 (5–463)
Hemoglobin (g/L)	71.3 (26–141)
Perpheral blood blast (%)	58.3 (2–98)

AML = acute myeloid leukemia, M0 = undifferentiated acute myeloblastic leukemia, M1 = acute myeloblastic leukemia with minimal maturation, M2 = acute myeloblastic leukemia with maturation, M4 = acute myelomonocytic leukemia, M5 = acute monocytic leukemia, M6 = acute erythroid leukemia, WBC = white blood cell count.

2. Patients and methods

2.1. General information

From January 2011 to December 2014, 237 patients with newly diagnosed AML were admitted to the hematology department of Fujian Medical University Union Hospital. According to the 2008 World Health Organization,[5] the patients were classified with standard MICM diagnostic classification. AML patients were analyzed for CR rate, RFS, and OS after induction chemotherapy (days 1–14). The peripheral blood blast clearance (PBBC) was used to calculate the time to circulating blast clearance. The time of the first disappearance of peripheral blood blast was defined as PBBC time, and the optimal cut-off was five days. The early-blast-clearance (EBC) group represented patients whose time to PBBC was less than 5 days, and the delayed-blast-clearance (DBC) group represented patients whose time to PBBC was more than or equal to 5 days. Other clinical parameters, including lactate dehydrogenase, the bone marrow cells, and other clinical hematology data, were collected. The clinical parameters of the AML patients are shown in Table 1. The study was approved by the Fujian Medical University Ethics Committee (approval number:FMUEC#107). All participants in the study gave informed consent to the use of blood and access to clinical information for research.

2.2. Induction chemotherapy and efficacy evaluation criteria

All patients were treated with "3 + 7 regimen" standard induction chemotherapy program (Ara-C 100–200 mg/sqm i.v. infusion on days 1–7, IDA 8 to 12 mg/sqm.i.v. infusion on days 1 to 3 or DNR 45 to 90 mg/sqm.i.v. infusion on days 1–3) induction chemotherapy for 2 courses. Peripheral blood analysis was performed from day 7 to day 14 of induction chemotherapy, while bone marrow aspiration was performed from day 21 to day 28. After 2 courses of induction chemotherapy, the achievement of CR and patients' clinical outcomes were assessed. CR was defined according to Cheson's criteria. OS was defined as the day 1 of induction chemotherapy to death or last contact. RFS was the time from CR to relapse, death, or last contact. Routine Follow-up was done till July 30, 2015.

2.3. Statistical analysis

All statistical analyses and graphics were performed by a computer using Statistical Production & Service Solution version 19.0 (SPSS Inc., Chicago, IL). Quantitative variables were described in the form of median and interquartile range. Qualitative variables were described as number and percent. For comparisons between the EBC group and the DBC group, the Chi-squared test or Fisher exact test was used to analyze categorical variables, and Student *t*-test was used to analysis quantitative variables. OS and RFS rates were estimated using the Kaplan–Meier method and compared by the log-rank test. A logistic regression model was constructed to analyze factors related to the CR rate. In the univariate analysis, the 2-tailed Chi-square or 2-tailed t-test was used to analyze statistical comparisons. In the multivariate analysis, Cox's proportional hazard regression model was used to identify the effects of multiple factors on RFS and OS. P values $< .05$ were considered as statistically significant.

3. Results

3.1. Prognostic impact of PBBC on CR rate

3.1.1. PBBC and CR rates. The patients were divided into two groups according to the time required for PBBC, and the CR rates between these two groups were compared (See Table 2).

Table 2

The relationship between the time to PBBC in 105 AML patients and their CR rate.

Day	CR rate of AML with PBBC < 5 d	CR rate of AML with PBBC ≥ 5 d	*P* value[a]
D_2	40/60 (66.7%)	29/45 (64.4%)	.487
D_3	42/65 (64.6%)	27/40 (67.5%)	.466
D_4	47/72 (65.3%)	22/33 (66.7%)	.536
D_5	58/78 (74.4%)	11/27 (40.7%)	.002*
D_6	62/94 (65.9%)	6/11 (54.5%)	.331
D_7	63/95 (66.3%)	5/10 (50.0%)	.244
D_8	65/97 (67.0%)	4/8 (50.0%)	.272
D_9	69/101 (68.3%)	0/4 (0%)	.012*
D_{10}	69/101 (68.3%)	0/4 (0%)	.012*

AML=acute myeloid leukemia, CR= complete remission, D_2=second day of induction chemotherapy, D_3=third day of induction chemotherapy, D_4=fourth day of induction chemotherapy, D_5=fifth day of induction chemotherapy, D_6=sixth day of induction chemotherapy, D_7=seventh day of induction chemotherapy, D_8=eighth day of induction chemotherapy, D_9=ninth day of induction chemotherapy, D_{10}=tenth day of induction chemotherapy, PBBC=peripheral blood blast clearance.

[a] Chi-square test.

* Significant at $P < .05$.

The CR rate of the EBC group was 74.4% (58/78). The CR rate of the DBC group was 40.7% (11/27). There was a significant difference between the two groups ($P = .002$). To further analyze EBC and DBC, the patients were divided into 2 groups (< 50% and ≥ 50%) according to the proportion of bone marrow immature cells before and after induction chemotherapy. Moreover, the group with a proportion of less than 50% belonged to the lower percent of myeloblast group, while the group with a proportion of more than 50% was the higher percent of myeloblast group. Analysis results showed that there were 48 cases (61.5%) of the EBC group and 3 cases (11.1%) of the DBC group in <50% group and there were 30 cases (38.5%) of the EDC group and 24 cases (88.9%) of the DBC group in >50% group. Finally, the myeloblast percent was significantly different between the EBC group and the DBC group ($P = .006$).

3.1.2. White blood cell count (WBC) and CR rate. Spearman bivariate analysis was used to measure the correlation coefficient between peripheral blood WBC counts from day 1 to day 14 of induction chemotherapy and CR rates. Analysis results show that the WBC counts of day 1, day 5, day 9 were significantly correlated with CR rate ($P < .05$). Moreover, the WBC counts of day 5 was strongest correlation with CR rate ($R = 0.437$, $P < .001$). ROC curve was used to analyze the relationship between WBC counts of day 5 and CR rate after induction chemotherapy. The results show that 1.25×10^9/L is a significant cut-off point (area under the curve = 0.761, the sensitivity of 77.9%) (Fig. 1). According to WBC counts on day 5 of induction chemotherapy, the patients were divided into two groups. Patients with WBC counts of less than 1.25×10^9/L was low-WBC-group, while those with WBC counts of more than 1.25×10^9/L was high-WBC-group. The CR rates between these 2 groups were significantly different ($\chi 2 = 50.25$, $P < .001$).

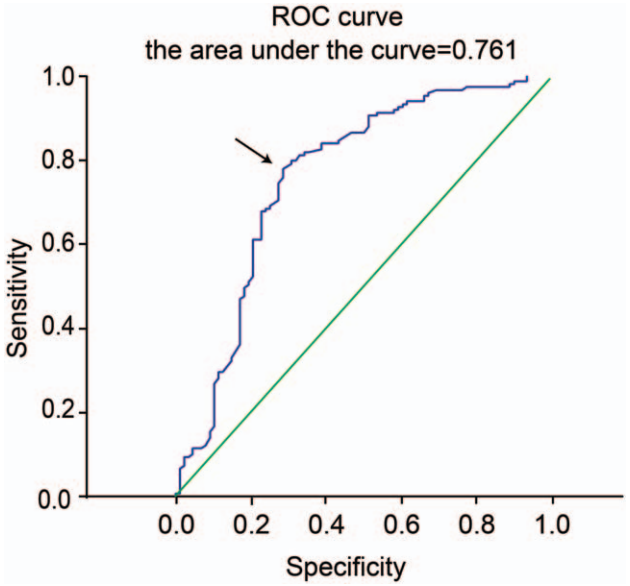

Figure 1. ROC curve analysis, arrow indicated the best sensitivity and specificity, corresponding WBC on the day 5 of induction was 1.25×10^9/L.

3.1.3. Univariate and multivariate analysis of clinical parameters impacting CR rates. Univariate analysis showed that age and cytogenetics were significantly related to CR rates ($P = .045$, .025) (Table 3). Multivariate analysis included age, time to PBBC, WBC counts of day 5, and cytogenetics (Table 4). The results showed that WBC counts of day 5 during induction chemotherapy and time to PBBC had statistically significant impacts on CR rates which are independent prognostic factors affecting CR rates in AML.

Table 3

The relationship between clinical parameters at the time of diagnosis and CR rate.

Prognostic factors	*P*-level
Age, yr	.045[a,*]
Gender	.058
Lactate dehydrogenase (U/L)	.417
WBC count ($\times 10^9$/L)	.347
Proportion of neutrophils (%)	.512
Proportion of mononuclear cells (%)	.342
Proportion of lymphocytes (%)	.563
Blood platelet count ($\times 10^9$/L)	.072
Hemoglobin (g/L)	.671
Peripheral blood blasts ($\times 10^9$/L)	.213
Cytogenetics	.025
	.025[a,*]

CR = complete remission, WBC = White blood cell count.

[a] Multivariate analysis

* Significant at $P < .05$.

Table 4

The relationship between prognostic factors and CR rate.

Prognostic factors	*P* value	OR (95%CI)
WBC of day 5 during induction	.001[a,*]	40.02 (3.79–44.29)
PBBC	.023[a,*]	6.00 (1.56–23.8)

CI = confidence interval, CR = complete remission, OR = odds ratio, PBBC = peripheral blood blast clearance, WBC = white blood cell count.
[a] Multivariate analysis.
[*] Significant at $P < .05$.

3.2. Survival analysis of AML

Kaplan-Meier Survival analysis showed that RFS and OS of the EBC group were significantly higher than those in the DBC group ($P = .026$, .001) (Fig. 2A and 2B). Meanwhile, other clinical parameters were analyzed by univariate analysis (Table 5). The multivariate analysis of other clinical parameters' impact on RFS and OS were carried out by Cox proportional hazards regression model (Table 6, Table 7). The results showed that the time to BPPC, age, and cytogenetics were the independent prognostic factors of RFS and OS in AML ($P < .05$).

4. Discussion

AML is a highly heterogeneous disease. The same treatment strategies and regimens may result in different outcomes for different AML patients. So it is required to develop individualized treatment strategies and programs based on their prognostic factors.

Cytogenetics and molecular biology abnormalities are the main prognostic factors for AML.[6,7] Among the 237 patients enrolled in this study, cytogenetic data were obtained from 209 cases. The results showed that CR, RFS, and OS were significantly worse in the high-risk group than in the intermediate-risk group. Multivariate analysis showed that cytogenetic is one of the most important independent predictors for poor outcomes in AML patients, which is consistent with previous reports. However, there are still some patients whose cytogenetic and molecular data are not available during the induction-chemotherapy. And a large proportion of AML patients possess normal karyotype (about 40% to 45%). The clinical heterogeneity of AML patients with normal karyotype needs to be better understood for the adjustment of their individualized treatment strategies to improve their prognosis.

Previous research has found that, during the process of induction chemotherapy in children with acute lymphoblastic leukemia, quick clearance of peripheral blast is one of the crucial

Table 5

The relationship between clinical parameters at the time of diagnosis and AML outcome.

Prognostic factors	RFS (P value)	OS (P value)
Sex	.63	.324
Age, yr	.012[a,*]	.431
WBC count ($\times 10^9$/L)	.312	.354
Platelet count ($\times 10^9$/L)	.45	.97
Hemoglobin (g/L)	.58	.43
Lactate dehydrogenase (U/L)	.63	.30
Cytogenetic	.021[a,*]	.016[a,*]
WBC of day 5 during induction	.064	.29

AML = acute myeloid leukemia, OS = overall survival, RFS = recurrence free survival, WBC = White blood cell count.
[a] Univariate analysis.
[*] Significant at $P < .05$.

Table 6

The relationship between prognostic factors and RFS.

Prognostic factors	*P* value	HR (95%CI)
Age	.01[a,*]	2.76 (1.3–5.8)
Cytogenetics	.024[a,*]	2.51 (1.2–5.6)
PBBC	.02[a,*]	3.11 (1.1–8.9)

CI = confidence interval, HR = hazard ratio, PBBC = peripheral blood blast clearance., RFS = recurrence free survival.
[a] Multivariate analysis.
[*] Significant at $P < .05$.

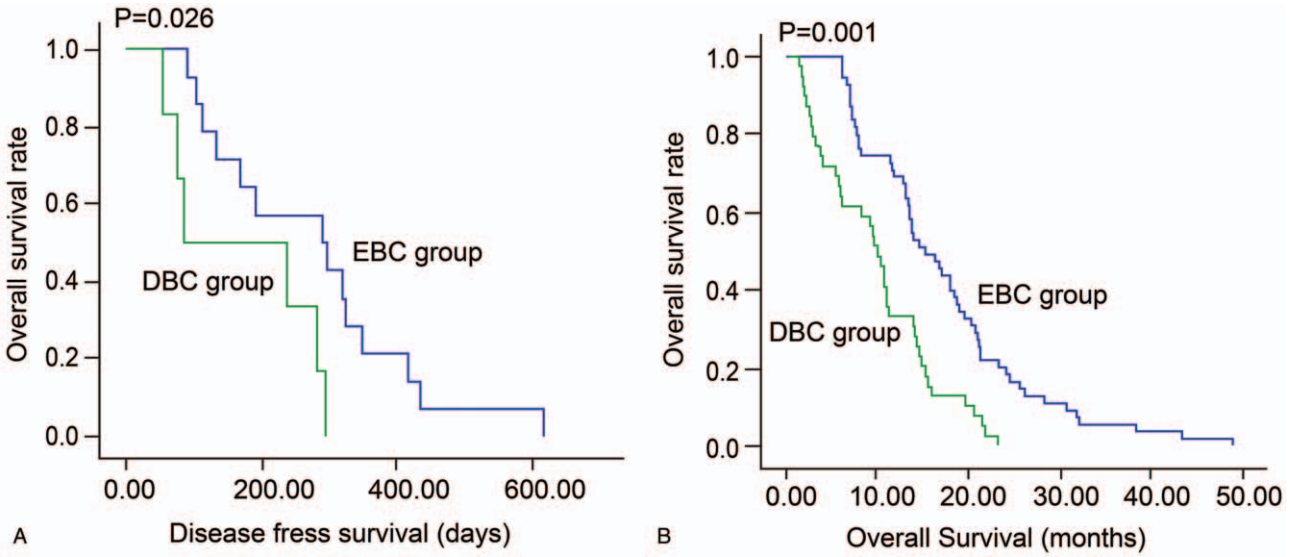

Figure 2. A. Kaplan-Meier survival analysis showed that the RFS of the EBC group was significantly higher than those in the DBC group ($P = .026$). 2B. Kaplan-Meier survival analysis showed that the OS of the EBC group was significantly higher than those in the DBC group ($P = .001$).

Table 7

The relationship between prognostic factors and OS.

Prognostic factors	*P* value	HR (95%CI)
Age	.002[a,*]	3.12 (1.2–6.3)
Cytogenetics	.03[a,*]	1.73 (1.1–7.8)
PBBC	.034[a,*]	4.14 (1.1–12.8)

CI = confidence interval, HR = hazard ratio, OS = overall survival, PBBC = peripheral blood blast clearance.

[a] Multivariate analysis.

[*] Significant at $P < .05$.

predictors for favorable outcomes.[8–12] It not only directly affects the CR rate but also relates to RFS and OS in acute lymphoblastic leukemia patients. Early work by Elliott demonstrated that *in vivo* chemosensitivity correlated with CR rate and RFS, but not OS in AML patients.[13–18] Therefore, we speculate that PBBC speed of AML patients during induction chemotherapy may also have a predictive value on the evaluation of efficacy and prognosis. In order to confirm the predictive value of the dynamics of peripheral blood cell counts in southeastern Chinese AML patient during induction chemotherapy, we analyzed 237 cases of newly diagnosed AML patients from January 2011 to December 2014. During the day 1 to day 14 of induction chemotherapy, the changes of peripheral blood cell counts and the prognosis parameters were analyzed. This study aimed to provide a clinical basis for the risk stratification of AML.

Our results showed that the time to PBBC has a predictive value for the short-term efficacy of AML. The time to PBBC reflects the chemosensitivity of leukemia cells in AML patients. Because induction chemotherapy not only kills leukemia cells but also kills hematopoietic stem cell at the same time leading to the decline of peripheral blood WBC count, hemoglobin, and platelet count. Statistical analysis showed that WBC of day 5 after induction was correlated with CR rate in AML patients. The ROC curve analysis confirmed that 1.25×10^9/L of the WBC count should be the significant cut-off point. In patients with the WBC count less than 1.25×10^9/L at day 5 of induction chemotherapy, the CR rate was significantly increased, which indirectly reflects the chemosensitivity of induction chemotherapy. Further analysis was done to confirm the value of the WBC counts in predicting CR rates. This study was done to compare the clinical characteristics of AML patients with CR and non-CR after one course of induction chemotherapy. In AML patients with CR after one course of induction, bone marrow cell proliferation and the ratio of primitive cells of day 7 to day 14 after induction chemotherapy were lower in patients with CR after one course of induction than non-CR patients. After the first course of induction chemotherapy, for those patients whose WBC counts at day 5 of induction chemotherapy were less than 1.25×10^9/L, the percentage of primitive cells in the bone marrow decreased by more than 50% after day 7 to day 14 of induction chemotherapy and was more likely to achieve CR. While in those AML patients who have not achieved CR, WBC counts after day 5 of chemotherapy were more than 1.25×10^9/L, and the percentage of primitive cells in the bone marrow decreased by less than 50% after day 7 to day 14 of induction chemotherapy. These suggest that WBC counts on day 5 were significantly correlated with clinical efficacy. If the patient's WBC counts on day 5 was higher than 1.25×10^9, it indicates that this patient might has poor chemosensitivity, or the drug dose of induction chemotherapy was too low. So, we may need to increase the dose of chemotherapy in the following treatment. However, this study found that WBC counts on day 5 did not significantly correlate with RFS and OS. It is reasonable to speculate that the *adverse* side effects of induction chemotherapy in patients with lower WBC on day 5 are hematologic toxicity resulting in higher early mortality. Patients with WBC counts of less than 1.5×10^9/L on day 5 of induction chemotherapy require precautions for infection and severe complications to reduce early mortality.

We found that the time to PBBC is an important factor affecting the prognosis of AML ($P < .05$). Further analysis showed that the time to PBBC was significantly correlated with the percentage of primitive cells in the bone marrow during early period of induction chemotherapy ($P < .05$). The percentage of bone marrow primitive cells in the EBC group decreased by more than 50% during day 7 to day 14 of induction chemotherapy, while the percentage of bone marrow primitive cells in the DBC group decreased by less than 50%. Meanwhile, multivariate analysis showed that the time to PBBC was an independent prognostic factor affecting CR rate. This study further found that peripheral blood cell count change had a prognostic value for RFS and OS. The AML patient whose time to PBBC was less than 5 days underwent longer RFS and OS. Multivariate analysis also showed that the time to PBBC was an independent prognostic factor impacting RFS and OS. These results were obtained by retrospective analysis of 237 Chinese novel AML patients, which are consistent with the previous reports from different researchers and therefore certify the clinical value of the time to PBBC in AML patients. In summary, the time to PBBC in AML patients during induction chemotherapy can be used as a good prognostic parameter to evaluate the early efficacy and long-term survival for AML patients, especially for those with normal karyotype. It can also be used as a reference for guiding clinical decision-making and prognosis analysis. A larger study involving more patients from multi-centers would further confirm its clinical application.

In summary, we can monitor the peripheral blood cell count change in AML patients to initially assess the prognosis of AML upon clinical treatment to make individualized treatment strategies and programs as soon as possible to improve the prognosis of AML patients. The peripheral blood changes in day 5 of induction chemotherapy in AML, especially the time to PBBC, have independent prognostic value for CR rate, RFS and OS in AML patients. Although this study is only a single-center retrospective study, which needs to be further confirmed by the multicenter study, it is a feasible and straightforward prognostic parameter to evaluate the efficacy of induction chemotherapy in AML.

Acknowledgments

The authors thank Professor Xu Lin (Department of Pathology, Fujian Medical University Fuzhou, Fujian Province) for expert assistance with the data analysis.

We thank all of the patients and volunteers for their participation in this study.

Author contributions

Conceptualization: Yuanmao Huang, Yanni Wang, Jinggang Li, Shaoyuan Wang.

Data curation: Yuanmao Huang, Yanni Wang, Yang Li, Jinggang Li, Shaoyuan Wang.

Formal analysis: Yuanmao Huang, Yanni Wang, Yi Zheng, Yang Li, Jinggang Li, Shaoyuan Wang.
Funding acquisition: Yuanmao Huang, Shaoyuan Wang.
Investigation: Yuanmao Huang, Yanni Wang, Lili Pan, Yang Li, Shaoyuan Wang.
Methodology: Yuanmao Huang, Yanni Wang, Yang Li, Shaoyuan Wang.
Project administration: Yuanmao Huang, Yanni Wang, Shaoyuan Wang.
Resources: Yuanmao Huang, Yanni Wang, Yi Zheng, Shaoyuan Wang.
Software: Yuanmao Huang, Yanni Wang, Lili Pan, Shaoyuan Wang.
Supervision: Yuanmao Huang, Yanni Wang, Lili Pan, Shaoyuan Wang.
Validation: Yuanmao Huang, Yanni Wang, Yi Zheng, Shaoyuan Wang.
Visualization: Yuanmao Huang, Yanni Wang, Yi Zheng, Shaoyuan Wang.
Writing – original draft: Yuanmao Huang, Yanni Wang, Shaoyuan Wang.
Writing – review and editing: Yuanmao Huang, Lili Pan, Shaoyuan Wang.

References

[1] Dores GM, Devesa SS, Curtis RE, et al. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Blood 2012;119:34–43.
[2] Khan I, Altman JK, Licht JD. New strategies in acute myeloid leukemia: redefining prognostic markers to guide therapy. Clin Cancer Res 2012;18:5163–71.
[3] Liesveld J. Management of AML: who do we really cure? Leuk Res 2012;36:1475–80.
[4] Felicetto F, Salvatore P, Franco L. Clinically useful prognostic factors in acute myeloid leukemia. Hematology 2008;66:181–93.
[5] Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114: 937–51.
[6] Ho PA, Kutny MA, Alonzo TA, et al. Leukemic mutations in the methylation-associated genes DNMT3A and IDH2 are rare events in pediatric AML: a report from the Children's Oncology Group. Pediatr Blood Cancer 2011;57:204–9.
[7] Balgobind BV, Hollink IH, Arentsen-Peters ST, et al. Integrative analysis of type-I and type-II aberrations underscores the genetic heterogeneity of pediatric acute myeloid leukemia. Haematologica 2011;96:1478–87.
[8] Gajjar A, Ribeiro R, Hancock ML, et al. Persistence of circulating blasts after 1 week of multiagent chemotherapy confers a poor prognosis in childhood acute lymphoblastic leukemia. Blood 1995;86:1292–5.
[9] Schrappe M, Reiter A, Riehm H. Cytoreduction and prognosis in childhood acute lymphoblastic leukemia. J Clin Oncol 1996;14:2403–6.
[10] Beldjord K, Chevret S, Asnafi V, et al. Oncogenetics and minimal residual disease are independent outcome predictors in adult patients with acute lymphoblastic leukemia. Blood 2014;123:3739–49.
[11] Manabe A, Ohara A, Hasegawa D, et al. Significance of the complete clearance of peripheral blasts after 7 days of prednisolone treatment in children with acute lymphoblastic leukemia: the Tokyo children's cancer study group study L99-15. Haematologica 2008;93:1155–60.
[12] Griffin TC, Shuster JJ, Buchanan GR, et al. Slow disappearance of peripheral blood blasts is an adverse prognostic factor in childhood T cell acute lymphoblastic leukemia: a Pediatric Oncology Group study. Leukemia 2000;14:792–5.
[13] Elliott MA, Litzow MR, Letendre L, et al. Early peripheral blood blast clearance during induction chemotherapy for acute myeloid leukemia predicts superior relapse-free survival. Blood 2007;110:4172–4.
[14] Vainstein V, Buckley SA, Shukron O, et al. Rapid rate of peripheral blood blast clearance accurately predicts complete remission in acute myeloid leukemia. Leukemia 2014;28:713–6.