Differentiation Syndrome and Coagulation Disorder – Comparison between treatment with Oral and Intravenous Arsenics in Pediatric Acute Promyelocytic Leukemia.

Jie-si Luo[1], Xiao-Li Zhang[1], Dan-Ping Huang[1], Yi-Qiao Chen[2], Wu-Qing Wan[3], Huirong Mai[4], Hui-Qin Chen[5], Hong Wen[6], Ri-Yang Liu[7], Guohua Chen[8], Yu Li[1], Xue-Qun Luo[1], Yan-Lai Tang[1], and Li-Bin Huang[1]

[1]Sun Yat-sen University First Affiliated Hospital
[2]Department of Pediatrics Fujian Medical University Union Hospital Fuzhou Fujian China
[3]The Second Xiangya Hospital of Central South University
[4]Shenzhen Children's Hospital
[5]Third Affiliated Hospital of Sun Yat-Sen University
[6]Department of Pediatrics The First Affiliated Hospital of Xiamen University Xiamen Fujian China
[7]Department of Pediatrics Huizhou Municipal Central Hospital Huizhou Guangdong China
[8]Department of Pediatrics First People's Hospital of Huizhou Huizhou Guangdong China

June 2, 2022

Abstract

Background: Realgar-Indigo naturalis formula (RIF) containing A $_4$S $_4$ as a major ingredient is an oral arsenic available in China. The efficacy of RIF on pediatric acute promyelocytic leukemia (APL) is comparable to arsenic trioxide (ATO). However, it remains to be explored that the effects of these two arsenicals on differentiation syndrome (DS) and coagulation disorder which are the two main life-threatening events in children with APL. **Procedure:** We analyzed 68 consecutive children with newly diagnosed APL involved in SCCLG-APL study (NCT02200978). Patients received all-trans retinoic acid (ATRA) on day 1 of induction therapy. ATO (0.16 mg/kg·d) or RIF (135 mg/kg·d) was administrated on day 5 after mitoxantrone on day 3 (non-high-risk group, NHR) or day 2-4 (high-risk group, HR). **Results:** The incidences of DS were 3.0% and 5.7% in ATO (n = 33) and RIF (n = 35) groups ($p = 0.590$), and 10.3% and 0% in patients with and without differentiation-related hyperleukocytosis, respectively ($p = 0.04$). The dynamic changes of WBC between the ATO and RIF groups were not statistically different. However, patients with high WBC counts or percentage of promyelocytes in peripheral blood tended to develop differentiation-related hyperleukocytosis. The improvement of coagulation indexes in the ATO and RIF groups had no statistical difference. Fibrinogen and prothrombin time had the quickest recovery rate. **Conclusions:** This study provides evidences that the incidence of DS and recovery of coagulopathy are similar whenever treating with RIF or ATO in children with APL.

INTRODUCTION

The long-term survival rate of acute promyelocytic Leukemia (APL) is exceeding 90% with contemporary treatment combining arsenic compounds, all-transretinoic acid (ATRA) and anthracycline-based chemotherapy (CHT).[1-4] However, early death (ED) is still a major issue in APL. The two main causes of ED are hemorrhage and differentiation syndrome (DS). The rate of early hemorrhagic death remains at about 5-10% in the clinical trial setting.[5] DS develops in up to 19% of the patients and DS-related death rate can be as

high as 5.7%.[5]Therefore, reducing the incidences of DS and hemorrhage is critical for further increasing the survival in patients with APL.

There are two arsenic compounds available for the treatment of APL in China: arsenic trioxide (ATO) and Realgar-Indigo naturalis formula (RIF). RIF is a traditional Chinese medicine containing realgar (As_4S_4) as well as Indigo naturalis, Radix salviae miltiorrhizae and Radix pseudostellariae which yield synergy anti-leukemia effects.[6] RIF has been proven as effective as ATO in treating childhood and adult APL, with the advantage of being an oral drug and reducing hospital stay.[1, 2]

The impact of RIF and ATO on the early complications may be different. In adult patients, RIF and ATO have similar effects on the recovery of coagulopathy, [7] but not on the kinetics of white blood cell count (WBC) ,[8] and RIF group has a higher peak WBC compared to ATO group during induction treatment.[8]Leukocytosis is an important factor in the development of DS. It is known that there are important distinctions between pediatric and adult patients with APL.[9] In fact, 84%-100% of pediatric patients with non-high risk (NHR) APL on ATO and ATRA induction therapy developed leukocytosis (WBC $> 10 \times 10^9$/L) and is much higher than 35%-47% in adult counterpart on the similar therapy.[10-15] To our knowledge, there is no report comparing the impacts of RIF and ATO on DS and hemorrhage in pediatric patients with APL. Therefore, the present study analyses these two main life-threatening events in pediatric patients with APL on induction therapy with SCCLG-APL (South China Children Leukemia Group-APL) protocol containing ATO or RIF, ATRA and mitoxantrone.

PATIETS AND METHODS

Eligibility

SCCLG-APL is a randomized, multicenter, and noninferiority trial and was conducted to determine whether intravenous ATO can be substituted by oral RIF in the treatment of pediatric APL [1], which was registered at www.clinicaltrials.gov as NCT02200978. Eligible patients were 16 years old or younger with newly diagnosed APL with confirmation of PML-RARα. Eight of hospitals enrolled in SCCLG-APL participated in present study. The study was approved by institutional review board and informed consent was obtained before treatment in accordance with the Declaration of Helsinki.

Induction Treatment

The details of treatment protocol were published.[1]During induction therapy, patients received ATRA at 25mg/(m^2·d) as soon as morphology diagnosis of APL was made. Mitoxantrone (MA) was administrated on day 3 (10mg/m^2) or day 2-4 (7mg/ (m^2·d) of ATRA treatment for NHR or high risk (HR) patients (diagnostic WBC count $>10 \times 10^9$/L) respectively. Once the diagnosis was genetically confirmed (5-6 days later), the patients were randomized to ATO or RIF group. ATO was administrated at 0.16mg/(kg·d) ([?]10 mg/day) intravenously over 12 hours daily, while RIF was given at 135mg/(kg*d) ([?]30 pills/day) orally three times daily, until complete remission was achieved.

When WBC exceeded $10x10^9$/L at the beginning of or during induction treatment, hydroxyurea was administrated at 100mg/(kg*d). Dexamethasone at 0.3 mg/(kg*d) was given if differentiation syndrome or ATRA-associated pseudotumor cerebri was suspected. Transfusions of platelet, and fresh-frozen plasma, cryoprecipitate and/or human fibrinogen (Fbg), were given for the aims of maintaining platelet counts (PLT) greater than 30 x 10^9/L, and Fbg greater than 1.5g/L, respectively. The use of heparin or low-molecular weight heparins for management of coagulopathy depended on doctors' clinical judgment.

Laboratory studies

The dynamic change of WBC and coagulation indexes including PLT, prothrombin time (PT), activated partial thromboplastin time (APTT), D-Dimer and Fbg were collected on the first day of visit (day 0) and after induction treatment (around day 4, 7, 10, 13, 16, 19, 22, 25 and 28). The percentage of promyelocyte in the bone marrow and peripheral blood were determined by microscopic examination by two experienced

physicians independently. Minimal residual disease (MRD) was monitored by qRT-PCR for detection of PML-RARα fusion gene.

Definition of Differentiation-Related Hyperleukocytosis and WBC Normalized Value

According to our previous study [1], differentiation-related hyperleukocytosis is defined as: WBC > 10 x 10^9/L in NHR group, and the maximum of WBC increases by over 30% compared with that at diagnosis (day 0) in HR group during induction treatment. To make the WBC data among patients comparable, the WBC counts have been normalized as the ratio between WBC on day X to WBC on day 0. Using this method of normalization, the WBC at day 0 would be 1 for all patients. The calculation formula is: WBC normalized value $=\frac{WBC\ (day\ X)}{WBC\ (day\ 0)}$.

Statistical analysis

Normally distributed variables were expressed as mean ± standard deviation (SD), while median (range) or median (interquartile range) was used to describe skewed variables. To compare the repeated measured data of the RIF and ATO groups, linear mixed model was used. Mann-Whitney U test were used for skewed data to compare between groups while two independent samples t test for normally distributed data. The comparison between Dichotomous variables was evaluated by the Chi-square (χ^2) test. ROC curve was used to define the cutoff values. IBM SPSS Statistics 21.0 was used for all statistical analysis.

RESULTS

Baseline Characteristics of Patients

From November 2011 to July 2019, data from 68 consecutive patients were retrospectively analyzed, including 33 in the ATO group and 35 in the RIF group. Patient characteristics are showed in Table 1. There were no significant differences in the baseline characteristics between the two groups except for a lower median APTT value in the RIF group, however, the median values of APTT were normal in both groups.

The Dynamic Change of WBC and the Incidence of DS

Combining statistics from NHR and HR patients, the overall dynamic trends of WBC in the ATO and RIF groups during the induction therapy were nearly consistent. Mixed linear model analysis showed that there was no statistical difference between the two groups, p=0.539 (Fig. 1).

Next, we separated NHR and HR patients to analyze. As shown in Fig. 2A, NHR patients in the RIF group had significantly higher WBC at admission and during induction treatment than in the ATO group. However, when the WBC normalized value was used to evaluate the trends of WBC, there was no significant deference between the two groups (Fig. 2C). The WBC of NHR patients from both groups increased in the first week of induction treatment and then decreased, probably due to the administration of MA on day 3. In HR patients, both the trends of WBC and the normalized values were not statistically different between the ATO and RIF groups (Fig. 2B and 2D). The WBC dropped rapidly after induction therapy, which may be related to the use of hydroxyurea at the beginning of induction therapy and the early use of mitoxantrone on the second day of induction therapy.

Moreover, there was no statistical difference in the incidences of moderate and severe DS between the two groups, which was 3.0% and 5.7% in the ATO and RIF group respectively ($p = 0.590$).

The Risk Factors for Differentiation-Related Hyperleukocytosis and DS

Patients with higher WBC counts or higher percentage of promyelocytes in peripheral blood tended to develop differentiation-related hyperleukocytosis (Table 2). As expected, moderate and severe DS occurred in 10.3% and 0% of patients with and without the differentiation-related hyperleukocytosis respectively ($p = 0.040$) (Table 2). Those patients who developed hyperleukocytosis have higher MRD after induction treatment ($p = 0.013$) (Table 2). High WBC at admission and high percentage of promyelocyte in peripheral blood were the risk factors predicting the development of hyperleukocytosis, with the cut-off values of 2.61×10^9/L and 26.5% respectively (Tables 2 and 3).

The Recovery of Coagulopathy

The recovery of coagulopathy was not statistically different between the ATO and RIF groups except for higher values of D-Dimer on day 12-14 in the RIF groups ($p< 0.05$) (Fig. 3 and Supplemental Table S1). In general, PT and Fbg recovered on day 3-5. PLT and D-Dimer levels needed longer time to recover. At weeks 1, 3 and 4, PLT returned to normal value (100×10^9/L) in 2.9%, 48.5% and 94.1% of the patients, and D-Dimer in 2.9%, 44.1% and 80.9% of the patients, respectively.

The incidences of bleeding and thrombus events were not statistically different between the ATO and RIF groups (Supplemental Table S2). There were 11 (33.3%) and 12 (34.3%) patients requiring heparin treatment in the ATO and RIF groups according to the judgment of clinicians respectively. In addition, the amount of platelets, plasma, and cryoprecipitate used was not statistical difference between the two groups (Supplemental Table S3).

DISCUSSION

We used the WBC normalized value to evaluate the trends of WBC and compare the WBC values at each time points because WBC at day 0 varied between patients. Our study shows that there is no significant deference in the trends of WBC between the RIF and ATO groups, either of NHR or HR patients. In our dada, only high WBC counts or percentage of promyelocytes in peripheral blood at diagnosis is associated with the development of differentiation-related hyperleukocytosis, and the cut off values are 2.61 $\times10^9$/L and 26.5%, respectively.

Wang et al. reported that adult patients treated with RIF had a significant higher peak WBC compared to those treated with ATO during induction treatment.[8] This is not confirmed in our cohort. The dose of RIF they used was 60 mg/(kg·d) which was lower than 135 mg/(kg·d) we used. The median plasma trough concentration of arsenic at steady-state (day 7) in their patients treated with RIF (0.33 μmol/L) was lower than that in those treated with ATO at 0.16 mg/(kg·d) (0.75 μmol/L)($p = 0.0048$).[2] It has been reported that arsenic at relatively high concentration (0.5 μmol/L or more) mainly induced apotosis while at low concentration induced differentiation of APL cells.[16] Therefore, it can be explained that higher peak WBC occurs in patients treated with low dose of RIF at 60 mg/(kg·d) than in patients treated with ATO at 0.16 mg/(kg·d). In our cohort, patients received ATO at 0.16 mg/(kg·d) or RIF at 135 mg/(kg·d). The plasma trough concentrations of arsenic are similar between the two groups on day 7, which were 0.51±0.16μmol/L (n=10) and 0.48±0.25μmol/L (n=9) ($p = 0.806$) (Data unpublished) respectively, and the trends of WBC were similar between the two groups. Our data show that WBC of NHR patients from both groups slightly increased in the first week of induction treatment, even though MA was administrated on day 3. The WBC of HR patients decreased significantly with more intense cytotoxic treatment including hydroxyurea administrated on day 0 and MA on day 2-4. It could be speculated that WBC might obviously increase during induction treatment without cytotoxic therapy.

An important question is raised based on our findings mentioned above. NHR APL in adults has been recently reported that can be successfully treated with a chemotherapy-free combination of ATRA and arsenic compound (RIF or ATO).[15] However, there is concern that the use of the two differentiating agents without chemotherapy may result in an increasing risk of leukocytosis and DS.[17]Previous studies indicated that the incidence of leukocytosis in pediatric patients with NHR APL treated on chemotherapy-free induction therapy was 84%-100% and much higher than 35%-47% in adult counterpart.[10-15] Recently, two multicenter clinical trials in pediatric APL, CCLG-APL2016 and SCCCG-APL, have been reported.[1, 18] One of the main differences of induction therapy between the two protocols is that the former used chemotherapy-free induction treatment with ATRA and arsenic in NHR patients while the latter used an additional dose of MA besides ATRA and arsenic. The incidence of DS was 6.8 times higher in CCLG-APL2016 group (41%) than in the SCCCG-APL group (6%). However, this difference cannot be explained by the difference in the proportion of HR patients between the two groups which is only 1.3 times more in the former than in the latter. Therefore, it strongly suggests that the safety of chemotherapy-free induction proved in adult with NHR APL is questionable in pediatric counterpart because of much higher incidences of leukocytosis and

DS in pediatric patients. A randomize clinical trial is on the way comparing the incidences of leukocytosis and DS between chemotherapy-free induction with RIF + ATRA and RIF + ATRA + one dose of MA in children with NHR APL (ChiCTR200003887).

In addition, the present study showed that the recovery of coagulopathy was not statistically different between the ATO and RIF groups except for higher values of D-Dimer on day 12-14 in the RIF groups. Our findings also support the view that Fbg and PT are the early and sensitive indicators of improvement in coagulopathy.[19]There was no statistical difference in the incidences of bleeding and thrombus events as well as the consumption of blood components between the two groups.

In conclusion, this study demonstrated the feasibility of replacing ATO at 0.16 mg/ (kg·d) with RIF at 135 mg/ (kg·d) in terms of the management of two main critical adverse events, DS and hemorrhage, in induction treatment in pediatric APL. Our findings also suggest that induction treatment with low-dose CHT such as anthracyclines may be important in pediatric APL, which may decrease the risk of differentiation-related hyperleukocytosis and DS during induction treatment. Patients with higher WBC counts or percentage of promyelocytes in peripheral blood tended to develop differentiation-related hyperleukocytosis, with the cut-off values of 2.61 $\times 10^9$/L and 26.5%, respectively.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ACKNOWLEDGEMENTS

This study was supported in China by the Science and Technology Planning Project of Guangdong Province (Grant No. 2014A020221008), the Science and Technology Planning Project of Guangzhou (Grant No. 201604020128), the Scientific research project of Guangdong Provincial Bureau of Traditional Chinese Medicine (Grant No. 20201056), the Medical Science and Technology Research Fund of Guangdong Province (Grant No. A2021352). We sincerely thank patients and their families for participating in this trial.

References:

1. Yang MH, Wan WQ, Luo JS, Zheng MC, Huang K, Yang LH, et al. Multicenter randomized trial of arsenic trioxide and Realgar-Indigo naturalis formula in pediatric patients with acute promyelocytic leukemia: Interim results of the SCCLG-APL clinical study. Am J Hematol 2018;93(12):1467-1473.

2. Zhu HH, Wu DP, Jin J, Li JY, Ma J, Wang JX, et al. Oral tetra-arsenic tetra-sulfide formula versus intravenous arsenic trioxide as first-line treatment of acute promyelocytic leukemia: a multicenter randomized controlled trial. J Clin Oncol 2013;31(33):4215-21.

3. Kutny MA, Alonzo TA, Gerbing RB, Wang YC, Raimondi SC, Hirsch BA, et al. Arsenic Trioxide Consolidation Allows Anthracycline Dose Reduction for Pediatric Patients With Acute Promyelocytic Leukemia: Report From the Children's Oncology Group Phase III Historically Controlled Trial AAML0631. J Clin Oncol 2017;35(26):3021-3029.

4. Iland HJPC, Group ALAL. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic Leukemia in the Australasian Leukemia and Lymphoma Group (ALLG) APML4 study: a non-randomised phase 2 trial. Lancet Haematol 2015;2(9):e357 - e366.

5. Kayser S, Schlenk RF, Platzbecker U. Management of patients with acute promyelocytic leukemia. Leukemia 2018;32(6):1277-1294.

6. Wang L, Zhou GB, Liu P, Song JH, Liang Y, Yan XJ, et al. Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia. Proc Natl Acad Sci U S A 2008;105(12):4826-31.

7. Zhu H, Guo Z, Jia J, Jiang Q, Jiang H, Huang X. The impact of oral arsenic and all-trans-retinoic acid on coagulopathy in acute promyelocytic leukemia. Leukemia Research 2018;65:14-19.

8. Wang F, Jia J, Wang J, Zhao T, Jiang Q, Jiang H, et al. The kinetics of white blood cell and the predictive factors of leukocytosis under oral or intravenous arsenic as the first-line treatment for acute promyelocytic leukemia. Leukemia Research 2017;61:84-88.

9. Kutny MA, Gregory J, Feusner JH. Treatment of paediatric APL: How does the therapeutic approach differ from adults? Best Practice & Research Clinical Haematology 2014;27(1):69-78.

10. Creutzig U, Dworzak MN, Bochennek K, Faber J, Flotho C, Graf N, et al. First experience of the AML-Berlin-Frankfurt-Munster group in pediatric patients with standard-risk acute promyelocytic leukemia treated with arsenic trioxide and all-trans retinoid acid. Pediatr Blood Cancer 2017;64(8).

11. Platzbecker U, Avvisati G, Cicconi L, Thiede C, Paoloni F, Vignetti M, et al. Improved Outcomes With Retinoic Acid and Arsenic Trioxide Compared With Retinoic Acid and Chemotherapy in Non–High-Risk Acute Promyelocytic Leukemia: Final Results of the Randomized Italian-German APL0406 Trial. Journal of Clinical Oncology 2017;35(6):605-612.

12. Lo-Coco F AGVM, dell'Adulto GIME, Group GAML, Leukemia SA. Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia. N Engl J Med 2013;369:111-21.

13. Zhang L, Zou Y, Chen Y, Guo Y, Yang W, Chen X, et al. Role of cytarabine in paediatric acute promyelocytic leukemia treated with the combination of all-trans retinoic acid and arsenic trioxide: a randomized controlled trial. BMC Cancer 2018;18(1):374.

14. Zhu HH, Huang XJ. Oral arsenic and retinoic acid for non-high-risk acute promyelocytic leukemia. N Engl J Med 2014;371(23):2239-41.

15. Zhu HH, Wu DP, Du X, Zhang X, Liu L, Ma J, et al. Oral arsenic plus retinoic acid versus intravenous arsenic plus retinoic acid for non-high-risk acute promyelocytic Leukemia: a non-inferiority, randomised phase 3 trial. Lancet Oncol 2018;19(7):871-879.

16. Chen GQ, Shi XG, Tang W, Xiong SM, Zhu J, Cai X, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): I. As2O3 exerts dose-dependent dual effects on APL cells. Blood 1997;89(9):3345-53.

17. Abedin S, Altman JK. Acute promyelocytic leukemia: preventing early complications and late toxicities. Hematology Am Soc Hematol Educ Program 2016;2016(1):10-15.

18. Zheng H, Jiang H, Hu S, Liao N, Shen D, Tian X, et al. Arsenic Combined With All-Trans Retinoic Acid for Pediatric Acute Promyelocytic Leukemia: Report From the CCLG-APL2016 Protocol Study. J Clin Oncol 2021:JCO2003096.

19. Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. Blood 2009;114(25):5126-35.

20. Ossenkoppele G, Schuurhuis GJ. MRD in AML: does it already guide therapy decision-making? Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):356-365.

21. Benjamini O, Dumlao TL, Kantarjian H, O'Brien S, Garcia-Manero G, Faderl S, Jorgensen J, Luthra R, Garris R, Thomas D, Kebriaei P, Champlin R, Jabbour E, Burger J, Cortes J, Ravandi F. Phase II trial of hyper CVAD and dasatinib in patients with relapsed Philadelphia chromosome positive acute lymphoblastic leukemia or blast phase chronic myeloid leukemia. Am J Hematol. 2014 Mar;89(3):282-7.

Figure legends:

Figure 1. The dynamic changes of median WBC during induction treatment for ATO and RIF group.

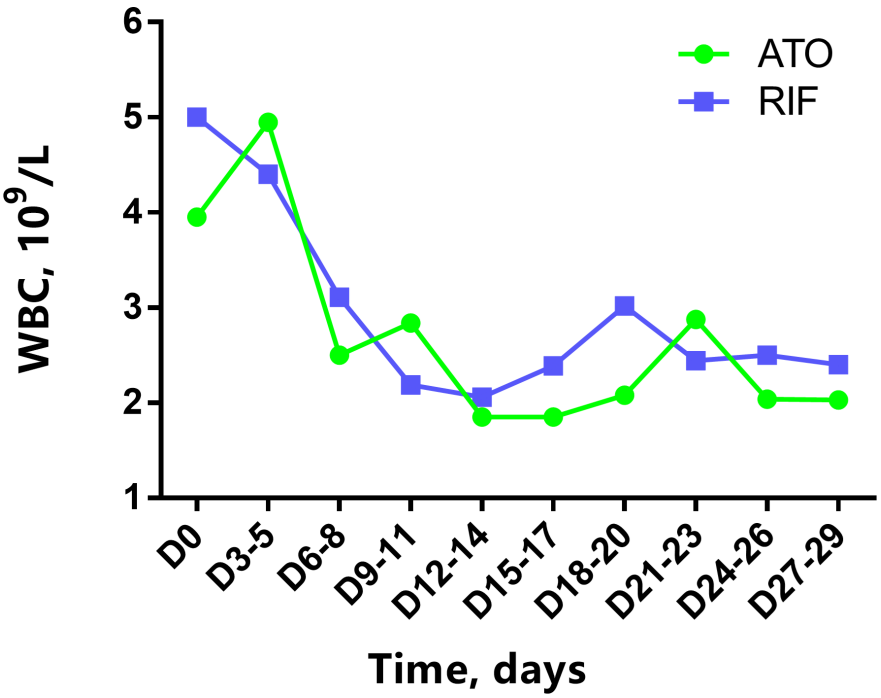
The WBC counts at different time points were compared using Mann-Whitney U test, all $p > 0.05$. The mixed linear model was used to analyze the overall dynamic trend of the two groups, $p = 0.539$.

Figure 2. The comparison of dynamic changes of median WBC count and median WBC normalized value between ATO and RIF group by risk stratification.

(A)In NHR group: There were statistically differences in WBC count between the ATO and RIF group at five time points. They are D0, Day 6-8, Day 12-14, Day 15-17 and Day 18-20 ($p = 0.047$, $p = 0.034$,$p = 0.035$, $p = 0.044$ and $p = 0.031$, separately). Using mixed linear model to analyze the overall dynamic trend of ATO and RIF groups, $p = 0.004$. (B)In HR group: The overall dynamic trend between ATO and RIF group was compared by mixed linear model, $p = 0.404$. Using Mann-Whitney U test to compare the WBC count at different time points, all p value > 0.05 between ATO and RIF group. (C)In NHR group: Comparison in the dynamic trend of WBC normalized value between ATO and RIF groups by mixed linear model,$p = 0.480$. Mann-Whitney U test was used to compare the WBC normalized value at different time points, $p > 0.05$. (D)In HR group: The overall dynamic trend of WBC normalized value was compared between ATO and RIF, $p = 0.379$. WBC normalized values at different time point were compared using Mann-Whitney U test, all$p$ value > 0.05.

Figure 3. The dynamic trend of coagulation data in ATO and RIF group.

All coagulation data in figure are showed as median with interquartile range. (A), (C) and (D): Mann-Whitney U test was used to compare the difference of PLT, PT and Fbg between the two groups at each time point, all $p > 0.05$. Using the mixed linear model to compare the recovery trend between ATO and RIF group, the $p$values of PLT, PT and Fbg were 0.352, 0.277 and 0.353 respectively. (B): D-Dimer on Day 12-14 ($p = 0.033$) showed slower recovery in RIF group. However, the p value of the dynamic trend calculated by mixed linear model was 0.285.



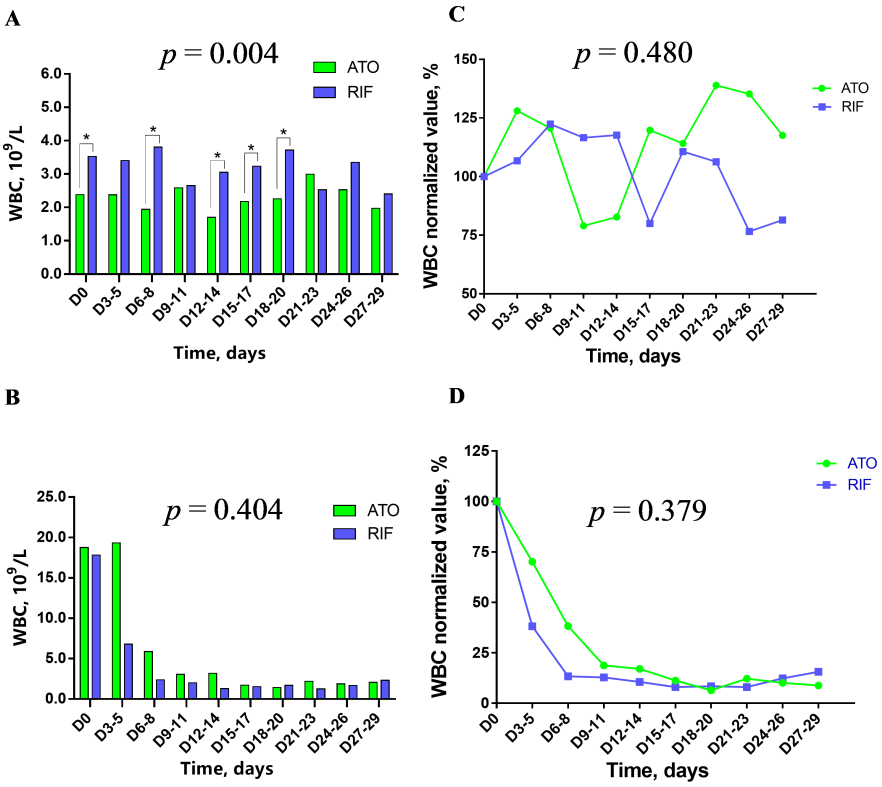
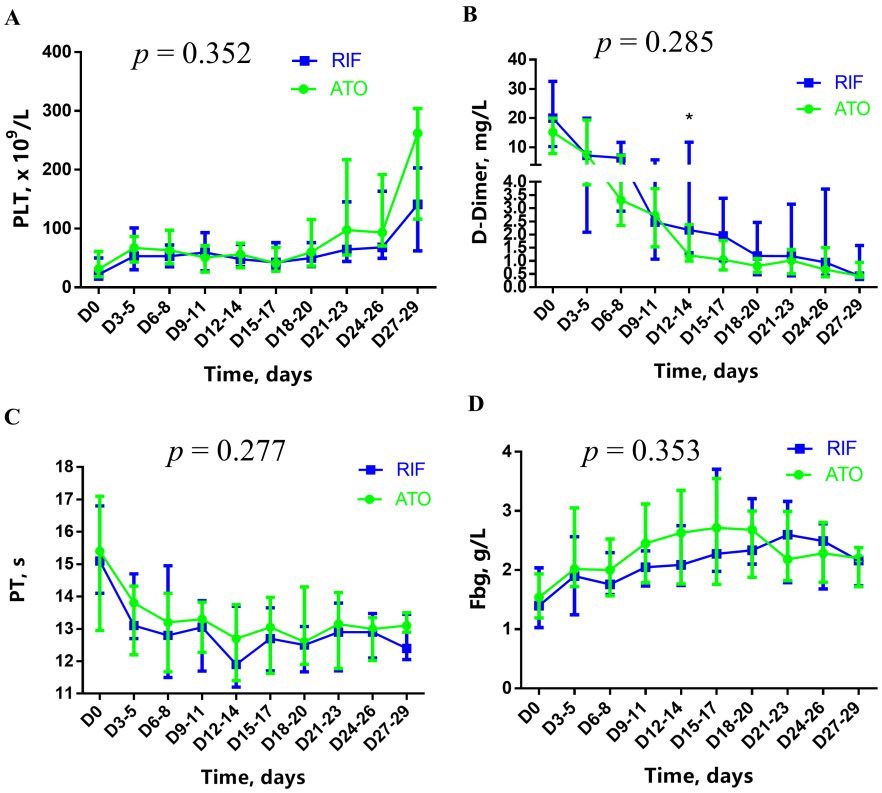


Figure 2



Hosted file

table_2_Jie-si_Luo_29052022.docx available at https://authorea.com/users/486734/articles/571583-differentiation-syndrome-and-coagulation-disorder-comparison-between-treatment-with-oral-and-intravenous-arsenics-in-pediatric-acute-promyelocytic-leukemia

Hosted file

table_1_Jie-si_Luo_29052022.docx available at https://authorea.com/users/486734/articles/571583-differentiation-syndrome-and-coagulation-disorder-comparison-between-treatment-with-oral-and-intravenous-arsenics-in-pediatric-acute-promyelocytic-leukemia

Hosted file

table_3_Jie-si_Luo_29052022.docx available at https://authorea.com/users/486734/articles/571583-differentiation-syndrome-and-coagulation-disorder-comparison-between-treatment-with-oral-and-intravenous-arsenics-in-pediatric-acute-promyelocytic-leukemia