Leukemia Research 61 (2017) 84–88

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

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

Fang Wang[a,b,1], Jin-Song Jia[a,1], Jing Wang[a], Ting Zhao[a], Qian Jiang[a], Hao Jiang[a], Hong-Hu Zhu[a,*]

[a] Peking University People's Hospital, Peking University Institute of Hematology, Beijing 100044, China
[b] Peking University International Hospital, Department of Hematology, Beijing, 102206, China

ARTICLE INFO

Keywords:
Acute promyelocytic leukemia
Arsenic
Leukocytosis
Differentiation syndrome

ABSTRACT

Objective: We aimed to compare the kinetics of white blood cell (WBC) and explore predictive factors of leukocytosis in non-high-risk acute promyelocytic leukemia (APL), with oral arsenic plus all-trans retinoic acid (ATRA) or intravenous arsenic trioxide (ATO) plus ATRA as a first-line treatment.

Methods: The absolute count, doubling time and peak time of WBC were analyzed in 64 newly diagnosed non-high-risk APL patients who were treated with different induction regimens containing either oral Realgar-indigo naturalis formula (RIF) (n = 35) or ATO (n = 29). The end points were the dynamic changes of the WBC counts during induction. The time points started at day 1 and were selected over 3-day intervals for 28 days.

Results: Among the 64 included patients, the median initial and peak WBC counts were 1.78 × 10^9/L (range 0.31–9.89) and 12.16 × 10^9/L (range 1.56–80.01), respectively. The incidence of differentiation syndrome was 9.38%. The dynamic changes in leukocytosis showed a single peak wave in all the patients, and the median time to peak was 10 (range 2–26) days. A higher WBC count was observed in the RIF group than in the ATO group after 10 days of treatment (9.22 × 10^9/L *vs.* 4.10 × 10^9/L, $p = 0.015$). Patients with the peak WBC count > 10 × 10^9/L had a shorter WBC doubling time compared to patients with a lower peak WBC (RIF group 4 days *vs.* 7 days, $p = 0.001$; ATO group 4.5 days *vs.* 23 days, $p = 0.002$). Univariate and multivariable analyses showed that the doubling time of WBC is an independent factor for the peak WBC count.

Conclusion: Different kinetics of WBC proliferation were observed during induction with oral arsenic plus ATRA and ATO plus ATRA. The doubling time of WBC is an important independent factor for predicting the peak WBC count.

1. Introduction

The combination of all-trans retinoic acid (ATRA) and arsenic has become the first-line treatment for acute promyelocytic leukemia (APL) and has transformed this disease from a poor prognosis to the most frequently curable acute leukemia [1–4]. However, early death is a major cause of induction failure [1–8]. Differentiation syndrome (DS) is a serious and life-threatening complication with mortality as high as 30% in the absence of early clinical intervention [1,3]. Several studies have found that leukocytosis is an important factor in the development of DS—especially among patients with a peak white blood cell (WBC) count greater than 10 × 10^9/L [3–7,9–10]. Studies of leukocyte proliferation kinetics during APL induction therapy may be important in predicting and preventing DS. However, there are no comprehensive studies that have explored WBC kinetics and risk factors for leukocytosis for APL patients with arsenic plus ATRA as a front-line treatment.

In the present study, we retrospectively analyzed a randomized controlled study (APL07) to describe the WBC kinetics in the first-line treatment of APL with either oral arsenic plus ATRA or intravenous arsenic trioxide (ATO) plus ATRA and attempted to explore risk factors for leukocytosis [11].

2. Methods

2.1. Patient selection and treatment

Between November 2007 and September 2011, 64 hospitalized patients aged 15–59 years old with newly diagnosed non-high-risk APL

* Corresponding author at: Peking University People's Hospital, Peking University Institute of Hematology, No. 11 Xizhimen South St, Beijing, 100044, China.
E-mail address: zhuhhdoc@163.com (H.-H. Zhu).
[1] Contribute equally to this study.

http://dx.doi.org/10.1016/j.leukres.2017.09.006
Received 8 June 2017; Received in revised form 9 September 2017; Accepted 11 September 2017
Available online 14 September 2017

Table 1
Demographic and baseline characteristics on admission of patients with RIF and ATO treatment.

Characteristic	Total patients (n = 64)	RIF group (n = 35)	ATO group (n = 29)	*p* value
Age, years (range)	34.6(15–59)	33(16–59)	37(15–59)	*0.377*
Male, n (%)	40(62.50)	22(62.86)	18(62.07)	*1.000*
BMI, kg/m^2 (range)	24.44(18.04–31.22)	24.44(8.04–31.22)	24.44(19.53–30.67)	*0.254*
Initial WBC count, × 10^9/L (range)	1.78(0.31–9.89)	1.62(0.61–9.89)	2.21(0.31–8.14)	*0.462*
< 5.0	54(84.38)	29(82.86)	25(86.21)	
5.0–10.0	10(15.62)	6(17.14)	4(13.79)	*1.000*
Initial platelet count, × 10^9/L (range)	38(6.00–179.20)	36.5(6.00–179.20)	40.4(8.20–164.60)	*0.856*
≥40	30(46.88)	15(42.86)	15(51.72)	*0.616*
< 40	34(53.12)	20(57.14)	14(48.28)	
The peak WBC count, × 10^9/L (range)	12.16(1.56–80.01)	13.93(2.16–80.01)	8.52(1.56–44.93)	*0.175*
< 10.0	30(46.88)	13(37.14)	17(58.62)	
10.0–20.0	16(25.00)	11(31.43)	5(3.45)	*0.208*
> 20.0	18(28.12)	11(31.43)	7(24.13)	
The time to peak WBC count, days (range)	10(2–26)	10(2–20)	9(2–26)	*0.928*
Myeloblasts of peripheral blood, % (range)	30(0–82)	28(0.71–82)	30.5(0–81)	*0.925*
Myeloblasts of bone marrow, % (range)	84(19–96)	83(39–96)	86(19–93)	*0.562*
PML-RARA/ABL transcripts, % (range)	44.35(9.4–141.7)	46(11.3–141.7)	35.1(9.4–108.2)	*0.097*
Type of PML-RARA/ABL transcript, n (%)				
Long	46(71.87)	23(65.71)	23(79.31)	
Short	14(21.88)	8(22.86)	6(20.69)	*0.153*
Variant	4(6.25)	4(11.43)	0	
FLT3 internal tandem duplication, n (%)	7(10.93)	2(5.71)	5(17.24)	*0.230*
Cytogenetic features, n (%)				
Solo t(15;17) translocation	24(37.50)	12(34.29)	12(41.38)	
Additional abnormal translocation	10(15.63)	6(17.14)	4(13.79)	*0.858*
Normal karyotype	20(31.25)	11(31.43)	9(31.03)	
Differentiation Syndrome, n (%)	6(9.38)	2(5.71)	4(13.79)	*0.397*
Other treatment, n (%)				
Hydroxyurea	8(12.50)	6(17.14)	2(6.90)	*0.275*

(WBC count at diagnosis ≤10 × 10^9/L) who were enrolled in a randomized controlled trial (APL07) at our center were retrospectively analyzed [11]. There were 35 and 29 patients in the oral Realgar-indigo naturalis formula (RIF) group and ATO group, respectively. The distributions of the main clinical and biological features for each series are summarized in Table 1. This study was approved by the Institutional Review Board of the Peking University People's Hospital.

2.2. The kinetics of WBC

The doubling time of the WBC count was defined as the time required for the initial WBC count to double, a continuous variable. Several measures of the peripheral blood WBC count were evaluated, relative to the kinetics of the WBC count. These included the initial and peak counts, as well as the doubling time and maximum increase in the WBC counts. The recording time points were set at the first visit (day 1) and after treatment (day 4, day 7, day 10, day 13, day 16, day 19, day 22, day 25, and day 28). We then analyzed the extent of leukocytosis and the relationship between the kinetics of WBC with the use of either RIF or ATO. Finally, we evaluated whether some indexes could predict the extent of leukocytosis such that effective measures could be implemented as soon as possible to prevent the development of DS. The primary observation period was 28 days during induction therapy.

2.3. Diagnosis and treatment of DS

A DS diagnosis was made based on clinical and radiological features in individuals undergoing induction therapy with ATRA in the presence of at least three of the following signs and symptoms: (a) unexplained fever; (b) weight gain > 5 kg; (c) unexplained hypotension; (d) acute renal failure; and (e) acute respiratory distress with chest radiographs showing the presence of pulmonary infiltrates or pleuropericardial effusion [12]. Dexamethasone was used at a dose of 10 mg per day when DS occurred. No prophylactic treatment of DS was recommended. Additionally, mitoxantrone was given to all the patients at a dose of 1.4 mg/m^2 per day for 5 days to avoid excessive increase in WBC and overt DS. If the WBC count exceeded 10 × 10^9/L, hydroxyurea at a dose of 3 g per day was given until WBC decreased to 10 × 10^9/L.

2.4. Statistical analysis

The descriptive statistics sensitivity, specificity, and positive predictive value were calculated. Assessments of whether these parameters differed between the RIF and ATO groups were conducted using the Wilcoxon rank sum test. For the multivariable analysis, a logistic regression model was created to identify and evaluate significant factors that could predict the extent of leukocytosis. Receiver operator characteristic (ROC) curves representing the relationship between sensitivity and specificity were compared using a nonparametric approach. The classification performance of the estimated cutoff values was respectively assessed in the RIF and ATO groups and compared to the doubling time of the WBC count cutoff at 5 days and 8 days. The performance of using the doubling time of WBC for predicting the extent of leukocytosis in patients receiving either RIF or ATO was further assessed using a multivariate logistic regression model. Analyses were done using SPSS software 20.0 (SPSS Inc., Chicago, IL, USA), and *P* values < 0.05 were considered significant.

3. Results

This study enrolled 64 patients with non-high-risk APL at our center in China between November 2007 and September 2011 in a randomized trial (APL07 trial). Among these patients, 30 (46.88%) were low risk (platelets ≥40 × 10^9/L), and 34 (53.12%) were intermediate risk (platelets < 40 × 10^9/L). The median age of the entire cohort was 34.5 years old (range, 15–59 years), and 62.5% were male. The median initial WBC and platelet counts were 1.78 × 10^9/L (range, 0.31–9.89) and 38 × 10^9/L (range, 6–179), respectively. The overall incidence of DS was 9.38%. If the peak of WBC exceeded 10 × 10^9/L, the incidence of DS was as high as 11.8%, while if the peak of WBC was less than 10 × 10^9/L, the incidence of DS was 6.67%. The patient characteristics are provided in Table 1. Patients in the RIF group (n = 35) and the ATO