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Research paper

The impact of oral arsenic and all-trans-retinoic acid on coagulopathy in acute promyelocytic leukemia

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ABSTRACT

The aim of our study was to evaluate the impact of oral arsenic (the realgar-indigo naturalis formula, RIF) and all-trans retinoic acid (ATRA) on coagulopathy in acute promyelocytic leukemia (APL) compared with intravenous arsenic trioxide (ATO) and ATRA during induction. Mitoxantrone was added to all the patients at a dose of 1.4 mg/m^2 per day for 5–7 days. D-dimer levels, prothrombin time (PT), fibrinogen (Fbg) levels and the platelet count were comparably analyzed among 83 newly diagnosed APL patients treated with RIF (n = 45) or with ATO (n = 38). Since induction therapy with RIF and ATRA, the median levels of Fbg, PT and platelets were recovered to the normal range within 4 days, 10 days and 28 days, respectively. The last day of platelet and plasma transfusion was day 12 (range: 0–24 days) and day 3 (range: 0–27 days), respectively. Among the 42 patients with a disseminated intravascular coagulation (DIC) score = 4, the consumption of transfused platelets was less in the RIF group than that in the ATO group (P = 0.037). In the 17 patients with a DIC score < 4, prompt recovery of Fbg levels (P = 0.028) was observed in the RIF group compared with that in the ATO group (P = 0.401). RIF and ATO showed similar effects on the recovery of coagulopathy in APL patients. RIF had a potential beneficial effect in accelerating the recovery of thrombocytopenia and hypofibrinogenemia for subclinical DIC patients.

1. Introduction

Recently, the combination of all-trans retinoic acid (ATRA) and arsenic has become the first-line treatment for patients with newly diagnosed acute promyelocytic leukemia (APL) [1,2]. A high cure rate above 90% of APL patients has been demonstrated by several groups [3–8]. Although great improvement has been obtained, an early death (ED) rate of 5–11% because of hemorrhage has not changed in the past decades [9–11]. Therefore, promoting the recovery of coagulopathy as soon as possible is vital to decrease ED of APL.

The hemostatic laboratory parameters and change in the trend during ATRA with or without chemotherapy have been extensively studied [12–17]. Only limited data are available concerning the change in coagulation and fibrinolysis during dual induction by ATRA and arsenic trioxide (ATO) as the induction regimen of APL [18–20]. Using a protocol that included chemotherapy in patients with APL, we recently found that oral arsenic (the realgar-indigo naturalis formula, RIF) provided an outcome similar to that produced with intravenous arsenic trioxide [4]. Recently, we found the promising outcome could be obtained only using RIF and ATRA without chemotherapy in a pilot study [7]. Oral arsenic and ATRA as first-line treatment has been adopted in the Chinese guidelines for the diagnosis and treatment of APL (2014) [2].

Although oral arsenic has been widely used in China, its impact on the recovery of coagulopathy and thrombocytopenia is unclear. Therefore, we retrospectively analyzed the hemostatic parameters prior to treatment and assessed dynamic changes during induction therapy in patients with newly diagnosed APL involved in a randomized controlled trial (APL07).

2. Materials and methods

2.1. Patients

From November 2001 until July 2011, 83 hospitalized patients aged 15–59 years with newly diagnosed APL involved in a randomized controlled trial (APL07) at our center were analyzed [4]. There were 45 and 38 patients in the oral RIF and ATO groups, respectively. The

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Table 1
Characteristics of the Study Patients.

Variable	Patients (n = 83)	RIF (n = 45)	ATO (n = 38)
Age (years)	36 (15–59)	35 (15–59)	37 (15–59)
Gender			
Male	49	26	23
Female	34	19	15
White blood cell count ($\times 10^9$/L)	6.7 (0.31–45)	6.18 (0.6–34.6)	7.46 (0.31–45)
Hemoglobin level (g/L)	84.65 (45–154)	85 (45–141)	85.26 (48–154)
Platelet count ($\times 10^9$/L)	42.43 (7–164)	41.64 (7–139)	44.11 (10–164)
PT (s)	13.98 (10.6–20.1)	13.83 (10.6–18.7)	14.16 (11–20.1)
APTT (s)	28.61 (17.4–64.5)	29.26 (21.9–64.5)	27.95 (17.4–37)
Fibrinogen (mg/dl)	199.46 (42–575)	185.2 (42–433)	216.34 (49–575)
D-Dimer (ng/ml)	1746.11 (277–6607)	1853.13 (463–6607)	1648.26 (277–6503)
Myeloblasts as% of bone marrow	80.9 (19–96)	81 (39–96)	81.75 (19–95)
% of PML-RARα/ABL transcripts	48.58 (9.4–141.7)	50.97 (11.3–141.7)	45.7 (9.4–117.9)
Type of transcript			
Long	55	30	25
Short	14	12	12
Variant	4	3	1
FLT3 internal tandem duplication mutations			
Positive	10	4	6
Negative	59	35	24
Cytogenetic features			
Solo t (15;17) translocation	70	40	30
Additional abnormal translocation	13	5	8
Platelet infused (units)	4.36 (0–16)	4.2 (0–16)	4.55 (0–14)
Plasma infused (ml)	1207.23 (0–10800)	1164.44 (0–10800)	1257.89 (0–6400)
Last day of platelet transfusion	13 (0–29)	12 (0–24)	13 (0–29)
Last day of plasma transfusion	3 (0–33)	3 (0–27)	2.5 (0–33)

PT, prothrombin time; APTT, activated partial thromboplastin time.

distributions of the main clinical and biological features for each series are summarized in Table 1. The disseminated intravascular coagulation (DIC) score for all patients in this study was calculated using the overt DIC criteria of the International Society on Thrombosis and Hemostasis (ISTH) [21,22]. This study was approved by the Institutional Review Board of the Peking University People's Hospital.

Each patient was treated uniformly with either oral arsenic RIF (60 mg/kg/d) or intravenous ATO (0.16 mg/kg/d, maximum 10 mg/d) and ATRA (25 mg per square meter of body-surface area) as first-line target treatments. Mitoxantrone was added to all the patients at a dose of 1.4 mg/m^2 per day for 5 days on the fourth day of the treatment in patients with a white blood cell (WBC) count below 10×10^9/L or on the first day in patients with a WBC count above 10×10^9/L [4]. According to the induction regimens, APL patients were divided into two groups: the RIF group and the ATO group. In the meantime, the transfusion of platelets was administered with a target of keeping the platelet count over 30×10^9/L or clinically relevant bleeding occurred. The administration of fresh frozen plasma (FFP) was performed in patients with either a prolonged prothrombin time (PT) value > 3 s compared to normal or a fibrinogen level less than 150 mg/dl [23,24]. None of the study patients received anticoagulant prophylaxis.

2.2. Laboratory studies and clinical outcomes

Routine blood tests, including the WBC counts, hemoglobin, and platelet counts, were carried out on EDTA-anticoagulated blood samples using a Sysmex XE-5000 Hematology Analyzer (Sysmex, Kobe, Japan). The STA Compact Automated Hemostasis Analyzer (Diagnostica Stago, Gennevilliers, France) was used for detecting coagulation and fibrinolysis parameters, such as PT, activated partial thromboplastin time (APTT), fibrinogen (Fbg) levels (Clauss method), and D-dimer levels (Immuno-turbidimetric method). Fusion gene transcript levels from chromosome aberrations were analyzed by reverse transcription-polymerase chain reaction. The promyelocytic percentage was determined by microscopic examination of the bone marrow by two experienced physicians separately.

2.3. Statistical analysis

Markers of DIC (D-dimer, PT, Fbg, and platelet count) were assessed. Hemostatic variables were expressed in the median (range) format. The recording time points were set at the first visit (day 0) and after treatment (day 4, day 7, day 10, day 14, day 17, day 21 and day 28). Patients treated with oral RIF were compared with those treated with intravenous ATO for each of the coagulation and fibrinolytic assays at each time point using the Wilcoxon signed-rank test. Dichotomous variables were compared with Fisher's exact test χ^2 test. Univariate analysis was assessed using correlation tests. Multivariate analysis was performed using logistic regression to determine the independent factors among the factors shown to have significance using univariate analysis. A P-value < 0.05 was considered statistically significant. Statistical analysis was accomplished by SPSS software 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

In our study, abnormalities of the 83 newly diagnosed patients with APL in routine hemostatic variables include thrombocytopenia, hypofibrinogenemia, prolonged PT and elevated D-dimer levels, as shown in Table 1. The APTT median values were in the normal range. Elevated D-dimer levels were seen in all but one patient (82/83, 98.8%). The overall incidence of thrombocytopenia was as high as 92.8% (77/83) of patients. Hypofibrinogenemia and prolonged PT occurred in 60.2% (50/83) and 16.9% (14/83) of our patients, respectively. Twenty-four (28.9%) patients had an overt DIC (defined as the ISTH-DIC score ≥5) at presentation. All but one of the other patients showed a condition of subclinical DIC: 42 (50.6%) had a DIC score equal to 4, and 16 (19.3%) had a DIC score from 1 to 3. A cumulative score of 5 or more included reduced platelet counts (100%), elevated levels of D-dimer (100%) and hypofibrinogenemia (20/24, 83.3%), together with prolonged PT (13/24, 54.2%). Prolonged PT (92.8%, 13/14) and fibrinogen less than 100 mg/dl (83.3%, 10/12) were mainly present in overt DIC. Hemostatic abnormalities of patients with nonovert DIC mainly included elevated D-dimer levels (57/58, 98.3%), thrombocytopenia (53/58, 91.4%) and hypofibrinogenemia (30/58, 51.7%). Only one patient with nonovert DIC had prolonged PT.

3.2. Dynamic changes in hemostatic variables

The dynamic changes in principal hemostatic parameters during remission induction therapy included the following (Fig. 1): the median levels of Fbg increased to the normal range after 4 days of therapy and reached the highest level generally within the first 14 days. The median PT kept shortening progressively and had fallen within the normal range since day 10. The median levels of elevated D-dimers showed a relatively slow downtrend and remained elevated above the normal range throughout the observation period. The median platelet count was maintained over 30×10^9/L during treatment using platelet transfusion if necessary and a lower than normal range within 3 weeks