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Review Article

Advantages of arsenic trioxide combined with retinoic acid and chemotherapy in treating acute promyelocytic leukemia

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Abstract: Objective: To explore the efficacy of arsenic trioxide (ATO) combined with all-trans retinoid acid (ATRA) and chemotherapy in treating acute promyelocytic leukemia (APL). Methods: A total of 90 patients with APL admitted to our hospital from June 2012 to June 2018 were enrolled, of which 50 patients were treated with ATO combined with ATRA and chemotherapy as a research group, and the rest were treated with ATRA and chemotherapy as a control group. The following indexes of the two groups were compared: Complete remission (CR) rate, remission time (time for symptom amelioration, time for restoration of coagulation indexes, and duration of hyperleukocytosis), safety, 3-year OS (overall survival), disease-free survival (DFS), and biochemical indexes (white blood cell count, proportion of promyelocytic cells, liver function indexes, myocardial enzyme indexes, and blood lipid index). Results: Compared with the control group, the research group showed a significantly higher CR rate, experienced a significantly shorter remission time, with no increase in the incidence of adverse reactions. The research group also showed higher 3-year OS, DFS, and liver function indexes, and lower myocardial enzyme, but showed no significant difference in blood lipid index. Conclusion: ATO combined with ATRA and chemotherapy can improve the CR rate and survival rate of patients with APL and shorten patients' remission time.

Keywords: Arsenic trioxide, retinoic acid, chemotherapy, acute promyelocytic leukemia

Introduction

Acute promyelocytic leukemia (APL) is a distinct type of marrow-like leukaemia with a typical feature that differentiation of promyelocytic cells is blocked, resulting in excessive cell accumulation, and its etiology is related to chromosome translocation and gene fusion [1, 2]. The best control of API needs to be based on early diagnosis, which facilitates timely treatment and quick respond to complications caused by treatment. The current screening strategy is suspecting first and then followed with genetic diagnosis [3]. Thanks to the optimization of treatment scheme, the remission rate of APL has increased from 6% to 91%, and its mortality has dropped to about 9% [4, 5]. The standard therapeutic scheme for patients with APL, from chemotherapy to combination of all-trans retinoid acid (ATRA), arsenic trioxide, and chemotherapy, brings wonderful news for patients with APL, and contributes to transforming the lethal disease to a disease with a cure rate as high as 80% [6]. The pathological mechanism of APL involves the production of PML/RARA fusion protein caused by chromosome translocation. ATRA and ATO belong to cancer protein targeted therapy, and their mechanism of action is to induce hydrolysis of the fusion protein [7]. Targeted therapy has been extensively applied to APL, but the disease endpoints of patients are still quite different, which demands a research on the combination of targeted therapy, its corresponding curative effect and disease resistance activity [8].

ATO is a chemical agent able to induce apoptosis of various cancer cells, which has exhibited a great efficacy in patients with APL, and has also been applied to treat diseases including syphilis, psoriasis, and cancer [9-11]. ATO has different pharmacological effects on different diseases, but it has potential toxicity that may involve the liver, skin, kidney, heart, and blood, and its toxic effect may be related to its activation of apoptosis-promoting state of cells [12, 13]. ATO is usually combined with ATRA to treat APL at medium or low risk, which has demonstrated advantages over ATRA combined chemotherapy [14]. However, there are also reports that neither ATO-ATRA nor ATRA-chemotherapy has outstanding curative effect on patients with high-risk APL [15]. ATRA is also one of the first-line treatment methods for patients with APL, which is helpful to induce processes of cells including differentiation, growth stagnation, and apoptosis and can exert cell clearance capability by enhancing autophagy in infectious cells [16, 17]. One study has revealed that ATO-ATRA-chemotherapy has a promising application prospect in high-risk patients or patients with elevated white cell count (WCC) [4].

However, there are few studies at present on the efficacy of ATO-ATRA-chemotherapy and ATRA-chemotherapy in patients with APL, and their effects on the patients' indexes about the heart, liver, and blood. Therefore, we carried out the experiment and enrolled patients with APL at all levels of risk, with the goal of providing clinical reference for the treatment of APL.

Materials and methods

General materials

A total of 90 patients with APL admitted to the First Affiliated Hospital of Anhui Medical University from June 2012 to June 2018 were enrolled, of which 50 patients were treated through ATO combined with ATRA and chemotherapy as a research group, and the rest were treated with ATRA and chemotherapy as a control group. The research group consisted of 28 males and 22 female between 25 and 49 years old, with a median age of 33.96±5.21 years, and the control group consisted of 21 males and 19 females between 28 and 50 years old, with a median age of 34.54±4.96 years. This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University and was in accordance with Helsinki Declaration. All participants signed informed consent forms. The inclusion criteria: Patients diagnosed with APL according to pathology, patients at 18 years old or older, patients receiving the treatment for the first time, and those meeting the criteria of the APL risk stratification system [18]. The exclusion criteria: Patients with co-morbid malignant tumor, severe organ dysfunction or infectious disease, patients with mental disease or communication obstacle, patients who had taken drugs with potential influence on the indexes used in this study, pregnant women, lactating women, and those unwilling to receive a 3-year follow-up. Other general data in this study are shown in **Table 1**.

Treatment methods

Patients in the control group were treated as follows: Each patient orally took ATRA (14414-1, Chreagen Biotechnology Co., Ltd., Beijing, China) at 30-60 mg/d for 2-3 times, and then received chemotherapy when his/her relatively low white blood cell recovered to normal or coagulation abnormality was alleviated, and then was treated with the DA scheme: 40-60 mg daunorubicin (BP1695-NIP, Baiao Laibo Technology Co., Ltd., Beijing, China) and 100 mg cytarabine (12432, Chreagen Biotechnology Co., Ltd., Beijing, China) were given for the patient for 4 courses, and one course consisted of 1-3 d of treatment. If complete remission (RC) was observed in the patient, the treatment was stopped. The selection of the above dosage depended on the severity of the patient's condition or drug sensitivity.

Patients in the research group were treated as follows: ATO was adopted for each patient based on the treatment for the control group. Each patient was treated with ATO injection (1 g/L, 10 ml) (H19990191, Yida Pharmaceutical Co., Ltd., Harbin, China) added with 500 ml 5% glucose injection (H11020024, Zizhu Pharmaceutical Co., Ltd., Beijing, China) in intravenous drip once a day.

Outcome measures

CR rate: The CR rate was calculated according to the recorded number of patients with CR, and CR was evaluated according to the

Table 1. Baseline data of the two groups [n (%), mean ± SD]

Factor	n	Research group (n=50)	Control group (n=40)	χ^2/t	*P*-value
Sex				0.110	0.740
Male	49	28 (56.00)	21 (52.50)		
Female	41	22 (44.00)	19 (47.50)		
Age (Y)				0.998	0.318
<35	51	26 (52.00)	25 (62.50)		
≥35	39	24 (48.00)	15 (37.50)		
Average age (Y)	90	33.96±5.21	34.54±4.96	0.536	0.593
Risk degree				0.221	0.896
High risk	27	14 (28.00)	13 (32.50)		
Medium risk	44	25 (50.00)	19 (47.50)		
Low risk	19	11 (22.00)	8 (20.00)		
Azurophilic granule morphology				2.628	0.105
Coarse	74	40 (80.00)	34 (85.00)		
Fine	16	10 (20.00)	6 (15.00)		
Positive fusion gene				2.000	0.157
Long type	81	43 (86.00)	38 (95.00)		
Short type	9	7 (14.00)	2 (5.00)		
Chromosome examination results				0.121	0.728
Typical karyotype	59	32 (64.00)	27 (67.50)		
Additional karyotype or others	31	18 (36.00)	13 (32.50)		
Drinking history				0.151	0.697
No	34	18 (36.00)	16 (40.00)		
Yes	56	32 (64.00)	24 (60.00)		
Smoking history				0.321	0.571
No	42	22 (44.00)	20 (50.00)		
Yes	48	28 (56.00)	20 (50.00)		
Place of residence				0.438	0.508
Rural area	28	17 (34.00)	11 (27.50)		
Urban area	62	33 (66.00)	29 (72.50)		
CR rate (%)	90	48 (96.00)	33 (82.50)	4.500	0.034

Response Evaluation Criteria in Solid Tumours (RECIST) [19]. Time for symptom amelioration, time for restoration of coagulation indexes, and duration of hyperleukocytosis: The average values of the three indexes were adopted for study; Adverse reactions: Adverse reactions were judged according to the Common Terminology Criteria for Adverse Events (CT-CAE) released by the World Health Organization; Overall survival (OS) and disease-free survival (DFS): The patients were followed by 3 years through telephone, visiting, and medical record reviewing, and the starting point of evaluation was the day of beginning treatment. WCC and proportion of promyelocytic cells: The two indexes in the patients were measured before and after treatment, recorded, and then averaged, respectively. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), troponin I (TnI), creatine kinase-MB (CK-MB), triglyceride (TC), and cholesterol (TG): The indexes in the patients were determined after 4 courses of treatment or after treatment, and the values of them were averaged, respectively.

Determination methods

Elbow venous blood (5 mL) was sampled from each participant, placed in a EDTA-K2 vacuum test tube (YA1302, Hengfei Biotechnology Co., Ltd., Shanghai, China), and centrifuged at 1500×g and 4°C for 10 min, and the serum and

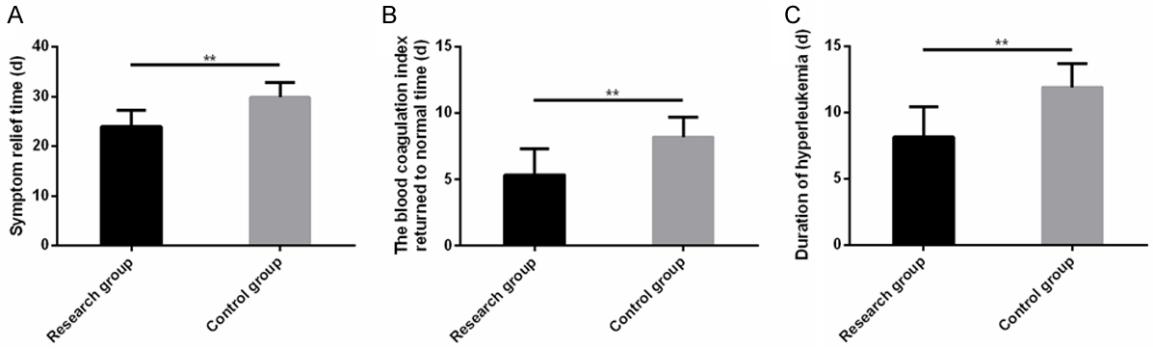

Figure 1. Remission of the two groups. A. The research group experienced significantly shorter time for symptom amelioration than the control group. B. The research group experienced significantly shorter time for restoration of coagulation indexes than the control group. C. The research group experienced significantly shorter duration of hyperleukocytosis than the control group. Note: ** indicates $P<0.01$.

Table 2. Incidence of adverse reactions in the two groups [n (%)]

Item	Research group (n=50)	Control group (n=40)	χ^2 value	*P*-value
Myelosuppression	42 (84.00)	36 (90.00)	0.692	0.405
Abnormal cardiac function	7 (14.00)	4 (10.00)	0.331	0.565
Abnormal liver function	14 (28.00)	10 (25.00)	0.102	0.749
Gastrointestinal reaction	8 (16.00)	6 (15.00)	0.017	0.897
Retinoic acid syndrome	6 (12.00)	7 (17.50)	0.544	0.461

plasma were separated and placed in a new EP tube and stored in a refrigerator at -70°C for later use. Indexes including WCC and ALT in the sampled blood were determined using a automated blood analyzer (XS-500, Newhuitong Biotechnology Co., Ltd., Nanjing, China), and the number of promyelocyte was counted and recorded under a microscope.

Statistical analysis

In this study, the data were analyzed and visualized into figures using GraphPad Prism 6 (GraphPad Software, San Diego, United States). The enumeration data were expressed as the number of cases/percentage (n/%), and compared between groups using the chi-square test. Data with theoretical frequency in chi-square test less than 5 were analyzed using the continuity correction chi square test. Measurement data were expressed as the mean ± standard error of mean (mean ± SEM), and compared between groups using the independent-samples T test, and compared within groups before and after treatment using the paired t test. The Kaplan-Meier method was applied to draw survival curves, and the Log-rank test was used to assess the difference in survival time between groups. $P<0.05$ indicates a significant difference.

Results

Baseline data

There was no significant difference between the two groups in sex, age, average age, risk degree, azurophilic granule morphology, positive fusion gene, chromosome examination results, drinking history, smoking history, and place of residence (all $P>0.05$), but there was significant difference between them in CR rate ($P<0.05$). See **Table 1**.

The remission of the research group was better than that of the control group

The research group experienced significantly shorter time for symptom amelioration, time for restoration of coagulation indexes, and duration of hyperleukocytosis than the control group (all $P<0.05$). See **Figure 1**.

The incidence of adverse reactions in the research group did not increase

The incidences of adverse reactions including myelosuppression, abnormal cardiac function, abnormal liver function, gastrointestinal reaction, and retinoic acid syndrome in the research group were lower than those in the control group, but the differences were insignificant (all $P>0.05$). See **Table 2**.

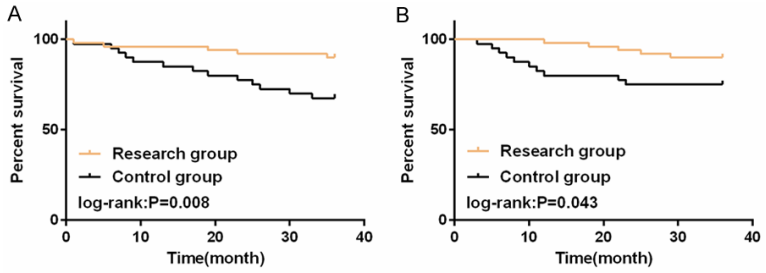

Figure 2. Long-term efficacy on the two groups. A. The 3-year OS of the research group was significantly higher than that of the control group. B. The 3-year DFS of the research group was significantly higher than that of the control group. Note: * indicates $P<0.05$ and ** indicates $P<0.01$.

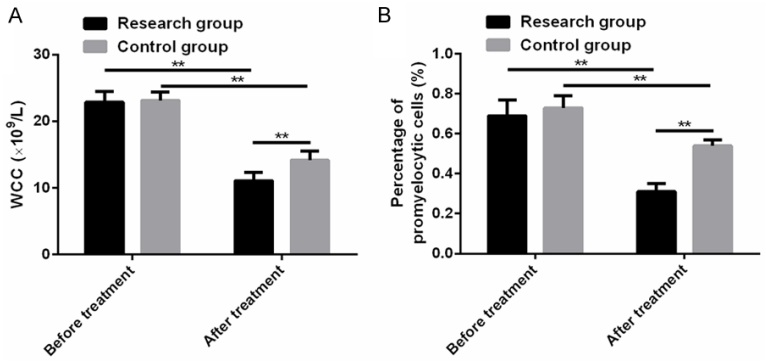

Figure 3. WCC and proportion of promyelocytic cells of the two groups. A. After treatment, the WCC of the research group was significantly reduced, and significantly lower than that of the control group. B. After treatment, the proportion of promyelocytic cells in the research group decreased significantly, and significantly lower than that in the control group. Note: ** indicates $P<0.01$.

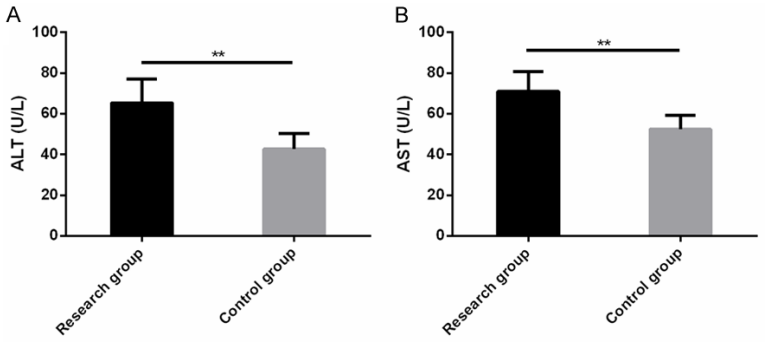

Figure 4. The liver function indexes of the two groups after treatment. A. After treatment, the research group showed significantly higher ALT than the control group. B. After treatment, the research group showed significantly higher AST than the control group. Note: ** indicates $P<0.01$.

The long-term efficacy on the research group was superior to that on the control group

The 3-year follow-up of this study was successfully completed, and none of the patients was lost to follow up. The 3-year OS and 3-year DFS of the research group were both significantly higher than those of the control group (90.00% *vs.* 67.50%, 90.00% *vs.* 75.00%, $P<0.05$). See **Figure 2**.

The improvement of WCC and proportion of promyelocytic cells in the research group was higher

Before treatment, there was no significant difference in WCC and proportion of promyelocytic cells between the two groups (both $P>0.05$), while after treatment, the two indexes of both group were significantly lowered, but the two in the research group were significantly lower than those in the control group ($P<0.05$). See **Figure 3**.

The liver function indexes of the research group were significantly higher than those of the control group after treatment

After treatment, the ALT and AST in the research group were both significantly higher than those of the control group (both $P<0.05$). See **Figure 4**.

The myocardial enzyme indexes of the research group were significantly lower than those of the control group after treatment

After treatment, the levels of TnI and CK-MB in the research group were both significantly lower than those in the control group (both $P<0.05$). See **Figure 5**.

There was no significant difference in blood lipid indexes between the research group and the control group after treatment

There was no significant difference in TG and TC levels between the research group and the

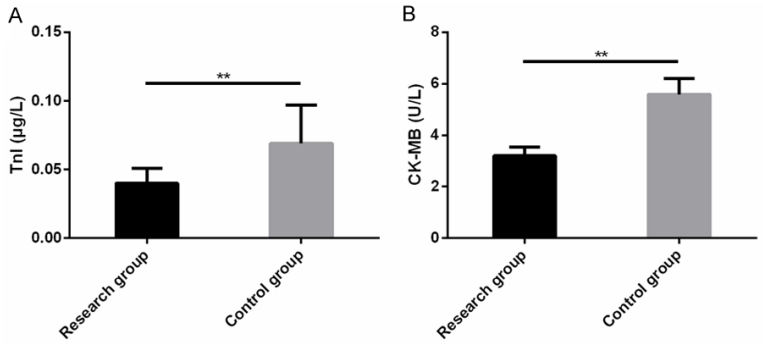

Figure 5. The myocardial enzyme indexes of the two groups after treatment. A. After treatment, the research group showed significantly lower TnI level than the control group. B. After treatment, the research group showed significantly lower CK-MB level than the control group. Note: ** indicates $P<0.01$.

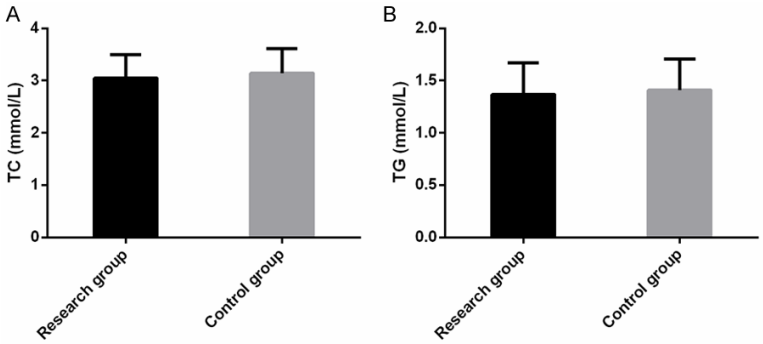

Figure 6. Blood lipid indexes of the two groups after treatment. A. There was no significant difference in TC between the research group and the control group after treatment. B. There was no significant difference in TG between the research group and the control group after treatment. Note: ** indicates P<0.01.

control group after treatment (both $P>0.05$). See **Figure 6**.

Discussion

APL is a malignant invasive bone marrow neoplasm. Despite a great advance in its treatment, there is still some controversy over it [20]. ATO-ATRA, as a dual differentiation therapy, has been supported by the national comprehensive cancer network and is suitable for patients with APL at moderate to low risk or with low WCC, but it is related to the high incidence of pseudotumor cerebri (50%) according to the report by Smith et al. [21]. There is also some controversy over the role of ATRA-chemotherapy as a maintenance therapy for APL not at high risk, but ATRA-chemotherapy can play a certain role against the resistance after ATO-ATRA treatment [3]. This study focused on the impact of ATO-ATRA-chemotherapy and ATRA-chemotherapy on patients with APL.

The effects of both ATO and ATRA on the pathological mechanism of APL are related to autophagy and apoptosis of APL cells, and their mechanism of action is both realized by the TAp73-DAPK2 pathway. The difference is that ATO mediates the pathway to affect apoptosis, while ATRA mediates it to induce autophagy [22]. In this study, patients in the research group were treated with ATO-ATRA-chemotherapy, while patients in the control group were treated with ATRA-chemotherapy. Based on comparison, it was found that the CR rate of the research group was significantly higher than that of the control group (96.00% *vs.* 82.50%). According to one report by Cull et al. [23], the CR rate of patients with APL treated with ATO or ATRA can exceed 90%, which is similar to the results of our study. We evaluated the remission time of the two groups in terms of symptoms, coagulation indexes, and white blood cell from the time of abnormality to the recovery. It was turned out that the research group performed better, because it experienced shorter duration of abnormality in the three aspects, suggesting that ATO-ATRA-chemotherapy may contribute to faster recovery of the patients. In addition, we evaluated the toxic reactions of the two groups after treatment mainly based on myelosuppression, abnormal cardiac function, abnormal liver function, gastrointestinal reaction, and retinoic acid syndrome, which are typical adverse reactions of targeted therapy for patients with APL [24, 25]. According to the results of our study, although patients in the research group additionally took ATO compared with those in the control group, they did not show increased incidence of adverse reactions, indicating that ATO-ATRA-chemotherapy is safe to a

certain extent. One study by Lo-Coco et al., [26] reported that patients with APL who received ATO-ATRA-chemotherapy suffered from more frequent QTc interval and abnormal liver function, while those who received ATRA-chemotherapy suffered more frequent pancytopenia, mucositis, and infection, indicating that both treatment schemes had certain toxic and side effects. We followed up the patients for 3 years, and found that the 3-year OS and DFS of the research group were significantly higher than those of the control group, indicating that ATO-ATRA-chemotherapy has an outstanding advantage in long-term survival. One study by Ma et al. [27] pointed out that compared with the ATO-ATRA group, the ATO-ATRA-chemotherapy group shows more prominent short-term and long-term efficacy advantages, which are different from the results of our study. WCC and the proportion of promyelocytic cells are the measurement indexes of APL severity, which can indirectly reflect the therapeutic effectiveness [28]. We evaluated some laboratory indexes of the patients, and found from the results of WCC and proportion of promyelocytic cells that the two indexes of the research group were significantly lowered after treatment, and were lower than those of the control group, which means that the treatment methods adopted for the research group may have more prominent curative effects. We determined liver function indexes (ALT and AST) of the two groups, finding that the research group showed higher levels of them, which implied that ATO-ATRA-chemotherapy may have some negative effects on the liver function of patients. One study has pointed out that the effects of ATO on patients' liver function may be related to AS3MT gene polymorphism, of which 35991 (rs-10748835) genotype may be a key influencing factor [29]. We also determined the myocardial enzyme indexes (TnI and CK-MB) of the two groups, and found that the research group showed lower levels of them after treatment, indicating that ATO-ATRA-chemotherapy had less negative impact on patients' cardiac function. One study by Wang et al. [30] has shown that the ATO-monotherapy group shows relatively high levels of TnI and CK-MB, while the ATO-ATRA-chemotherapy group does not show such a situation, which is different from the results of our study. One other study has reported that ATO has potential myocardial toxicity to patients with APL, and the mechanism may be related to the fact that ATO increases the level of myocardium enzyme and activates the anti-oxidation mechanism [31]. According to the results of this study, we suspected that the difference may be due to the fact that patients receiving ATO-ATRA-chemotherapy consumed less time to obtain CR, and used a smaller dosage of drug. One study by Breccia et al. [32] has revealed that body mass index (BMI) is a predictive index for relapse of APL, and TC and TG are strongly linked to high BMI. Therefore, we also evaluated the effects of the two treatment schemes on TC and TG of patients. It came out that there was no significant difference in TC and TG between the two groups, suggesting that ATO-ATRA-chemotherapy does not have additional effects on blood lipid of patients. One study by Cheng et al. [33] has revealed that ATO can change lipid metabolism during TG reverse transport by inhibiting liver X receptor β and enhancing the expression of cholesteryl ester transfer protein, which is contrary to our research results. It may be due to insufficient sample size and large individual difference of our study.

The innovation of this study lies in the more comprehensive inclusion of biochemical indicators such as liver function index, myocardial enzyme index, and serum lipids index for comparative evaluation of treatment schemes, which verifies that ATO-ATRA-chemotherapy has more advantages in treating patients with APL. However, there is still room for further study and further improvement in the study design. First of all, we can supplement the discussion on the risk factors affecting the poor prognosis of patients with APL. Second, we can supplement a molecular research on pharmacological mechanisms to explore specific regulatory mechanisms of targeted therapy and its influence on potential chemical resistance.

To sum up, ATO-ATRA-chemotherapy has certain advantages in remission time, safety, and survival rate in the treatment of APL, so it has a great clinical promotion value.

Disclosure of conflict of interest

None.

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