

Original Article

Effects of Yiqi Yangyin decoction in patients with Qi-Yin deficiency during bone marrow suppression following chemotherapy for acute leukemia

Ming Sun¹, Yeyun Che², Sheng Wang³

Departments of ¹Hematology, ²Neurosurgery, ³Laboratory, Linzi District People's Hospital, Zibo, China

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Abstract: Objective: To analyze the efficacy of Yiqi Yangyin Decoction (YYD) for patients with acute leukemia (AL) and Qi-Yin deficiency as well as bone marrow suppression. Methods: 79 patients with acute leukemia were retrospectively analyzed. All patients received chemotherapy and developed bone marrow suppression. They were randomly divided into observation group (OG) (n = 39) and control group (CG) (n = 40). After chemotherapy, the CG received Western medicine therapy. The OG received YYD. The symptom index, blood coagulation function, liver function, and renal function of the two groups were compared. Results: The symptom indices of the OG after 1, 2, and 3 weeks of treatment were lower than those of CG ($P < 0.05$). The APTT levels were significantly lower than those before treatment ($P < 0.05$) and the APTT level of OG was higher than that of CG ($P < 0.05$). After 3 weeks of treatment, the ALT and AST levels of the OG and the CG were increased ($P < 0.05$). The WBC levels was higher in the OG than that of CG after 1 and 3 weeks of treatment ($P < 0.05$). Conclusions: Yiqi Yangyin Decoction can relieve symptoms more quickly, improve coagulation function, increase the platelets and WBC levels, preserve liver and renal function, and exhibit low-frequency adverse reactions, high safety and good application prospect in AL patients with Qi-Yin deficiency and bone marrow suppression.

Keywords: Acute leukemia, chemotherapy, bone marrow suppression, Qi-Yin deficiency, Yiqi yangyin decoction, Chinese medicine

Introduction

Leukemia is one of TOP 10 malignant tumors. Acute leukemia (AL) is a cancer of hematopoietic stem cells characterized by the development of large numbers of immature lymphocytes. Hematopoietic cells undergo mutations during the differentiation phase, which leads to uncontrolled cell proliferation, differentiation, apoptosis and eventually malignant proliferation [1]. The clinical manifestations of AL include enlargement of the lymph nodes in the liver and spleen, fever, anemia, and bleeding, which directly threaten the patient's life [2].

Clinically, patients with AL must be treated immediately. The treatment options include supportive treatment, chemotherapy, and hematopoietic stem cell transplantation, of which chemotherapy is the most widely used method [3]. Chemotherapy can alleviate the condition of leukemia, but cannot completely cure it, and

there are obvious toxic side effects associated with chemotherapy, which affect the hematopoiesis and even lead to bone marrow suppression [4]. In patients with AL who developed bone marrow suppression, the white blood cell count decreases and the risk of infection increases. Hemoglobin levels can become low, causing anemia. In addition, low platelet count increases the incidence of bleeding, seriously impacting the quality of life [5]. Therefore, for these patients, other treatments need to be performed after chemotherapy. Western medicine usually suggested red blood cell or platelet transfusions, drugs that may increase WBC counts, etc. However, blood is a precious but limited resource, not all patients can be treated in time. Currently, clinical studies have found that TCM can effectively treat patients with myelosuppression after AL chemotherapy.

This study specifically analyzes the clinical efficacy of Yiqi Yangyin Decoction in patients with

Qi-Yin deficiency and bone marrow suppression following acute leukemia chemotherapy, exploring more useful treatment option.

Materials and methods

Data

79 cases of patients diagnosed as AL in our hospital were divided into observation group (OG) and control group (CG) according to random number table. The patients in OG ($n = 39$) aged 27-80 years, with 1-6 months of chemotherapy, 150-173 cm, 53-69 kg. The patients in CG ($n = 40$) aged 25-80 years, with 1-7 months of chemotherapy, 152-175 cm, 54-72 kg. (1) Inclusion criteria: patients who meet the diagnostic criteria for acute leukemia [6]; patients who developed bone marrow suppression following chemotherapy; patients who were diagnosed as Qi-Yin deficiency type; patients with complete clinical data, clear consciousness. The patients or their guardians were informed about the study procedures and written consent was signed and the study was approved by the hospital ethics committee. (2) Exclusion criteria: patients with severe heart, liver, kidney, lung, and brain diseases; patients who received other treatment options within one week before enrollment; patients who are allergic to the study drug; patients with poor compliance.

Methods

Both groups of patients received chemotherapy with the same chemotherapeutic drugs, regimens, and courses of treatment. The CG was additionally treated with antibiotics and drugs that increase WBC counts, including I.V. ceftazidime (H20013075, Qilu Pharmaceutical Co., Ltd.) + amikacin (H36020080, Jiangsu Wuzhong Pharmaceutical Group Co., Ltd.) and squalene tablets (H11022231, Beijing Great Wall Pharmaceutical Factory), 0.5 g (1 capsule), P.O. B.i.d. The treatment lasted for 3 weeks.

The patients in the OG were treated with Yiqi Yangyin Decoction after chemotherapy. The decoction consisted of 9 g divaricate saposhnikovia root, 15 g asparagus, 45 g astragalus, 9 g schisandra, 30 g coastal glehnia root, 12 g atractylodes Rhizome, 15 g Ophiopogon japonicus and 15 g Chinese yam. The herbs were cooked into 200 ml soup, 100 ml for morning drink after breakfast and 100 ml for evening

drink half an hour after dinner. The treatment lasted for 3 weeks.

The two groups received same supportive therapy. When the platelet count was $<10 \times 10^9/L$, platelet transfusion was performed; when the hemoglobin level was $<80 \text{ g/L}$, suspended red blood cells were transfused; when the white blood cells were $<1 \times 10^9/L$, leukocyte-enhancing drugs were used for treatment.

Observation index

Symptom index: A symptom index evaluation was performed before treatment, after 1 week, 2 weeks and 3 weeks of treatment. Symptoms included fatigue, shortness of breath, dizziness, spontaneous sweating, anorexia, dry stools, night sweats, dry throat and sphoria with feverish sensation in chest, palms and soles. Each symptom was scored 1-3 points, corresponding to mild, moderate, severe symptoms, and the total score of symptoms is 9-27 points. Higher points indicated more severe symptoms.

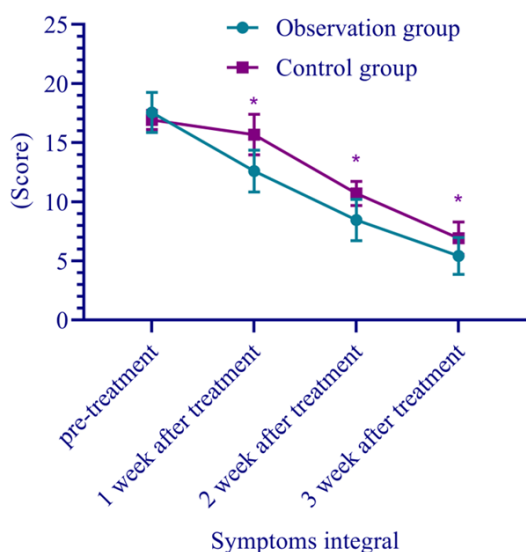
Coagulation function: Prothrombin time (PT), fibrinogen (FIB), and activated partial thromboplastin time (APTT) were measured before and 3 weeks after treatment. 5 ml of peripheral venous blood was drawn at these time points, and tested by an automatic hemagglutination instrument, and the operation was strictly performed according to the instructions.

Liver and renal function: The liver function and renal function of the two groups of patients were measured before treatment and after 3 weeks of treatment, including alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN) and urine creatinine (Creatinine, Cr). 5 ml of peripheral venous blood was collected, centrifuged for serum separation, and detected by an automatic biochemical analyzer.

Blood tests: The white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hemoglobin, Hb), and platelet count (PLT) of the two groups were measured before treatment, after 1 week and 3 weeks of treatment. Test method: Peripheral venous blood (5 mL) under fasting state in the morning was extracted at three time points, respectively. Within half an hour after collection, the above indicators were

Table 1. Comparison of general data between two groups ($\bar{x} \pm sd$)/[n (%)]

Data		Observation group (n = 39)	Control group (n = 40)	t/χ^2	P
Gender	Male	21 (53.85)	23 (57.50)	0.107	0.744
	Female	18 (46.15)	17 (42.50)		
Age (year)		53.62 \pm 15.49	55.13 \pm 16.84	0.415	0.680
Height (cm)		160.25 \pm 8.49	162.38 \pm 7.43	1.187	0.239
Weight (kg)		62.37 \pm 5.19	64.83 \pm 6.23	1.904	0.061
Duration of chemotherapy		2.89 \pm 1.05	3.32 \pm 1.26	1.646	0.104

**Figure 1.** Comparison of symptom indices between two groups. Before treatment, there was no significant difference in symptom indices between the two groups ($P>0.05$). After 1, 2 and 3 weeks of treatment, the symptom indices of the OG were significantly lower than those of the CG ($P<0.05$). * indicates $P<0.05$ for comparison between the two groups.

detected by the XN-A1 automatic hematology analyzer (Sysmex Corporation, Japan) and the matching reagent. The operation was carried out strictly in accordance with the kit instructions.

Statistical method

Statistical analysis was performed using SPSS22.0. Measurement data was expressed as mean \pm standard deviation, and inter-intra comparison was performed by independent sample t test. Count data was expressed as [n (%)], and was compared using χ^2 test. Multi-point data comparison was analyzed by ANOVA, F test. Figures were made by Graphpad Prism 8. $P<0.05$ indicates that the difference is statistically significant.

Results

Comparison of general data between two groups

There was no significant difference between two groups in terms of gender proportion, the average age, average height, average body weight and duration of chemotherapy ($P>0.05$) (Table 1).

Comparison of symptom indices between two groups

The symptom indices of the OG and CG were 17.52 \pm 3.62 points and 17.16 \pm 3.49 points before treatment; After 1 week of treatment, they scored 12.43 \pm 2.96 points and 15.75 \pm 3.02 points; The OG and CG scored 8.75 \pm 1.34 points and 10.64 \pm 1.75 points after 2 weeks of treatment; After 3 weeks of treatment, the symptom indices were reduced to 5.45 \pm 0.86 points and 6.95 \pm 1.12 points. After 1, 2 and 3 weeks of treatment, the symptom indices of the two groups were reduced, and they were statistically different compared with those before treatment ($P<0.05$). The OG showed significantly lower symptom indices than those of CG ($P<0.05$) (Figure 1).

Comparison of coagulation function between two groups

Before treatment, two groups showed no significant differences in coagulation function indices ($P>0.05$). After 3 weeks of treatment, the levels of PT, FIB, and APTT in the OG were not different from those before treatment ($P>0.05$); PT and FIB levels in the CG did not differ from those before treatment ($P>0.05$) while the levels of APTT were significantly lower than those before treatment ($P<0.05$). APTT level after 3 weeks of treatment in the OG was significantly higher than that of the CG ($P<0.05$) (Table 2).

Comparison of liver function between two groups

After 3 weeks of treatment, ALT levels were significantly higher than those before treatment in two groups ($P<0.05$); AST levels were not much different from those before treatment in two groups ($P>0.05$), and ALT and AST levels in the OG after 3 weeks of treatment were not different from the CG ($P>0.05$) (Table 3).

Effects of YYD for patients with AL

Table 2. Comparison of coagulation function before and after treatment ($\bar{x} \pm sd$)

Grouping	Time-points	PT (s)	FIB (g/L)	APTT (s)
Observation group (n = 39)	Before treatment	12.89 \pm 2.34	5.81 \pm 1.16	36.16 \pm 6.29
	3 weeks of treatment	12.34 \pm 3.05	4.73 \pm 1.23	36.75 \pm 5.08
Control group (n = 40)	Before treatment	12.15 \pm 1.89	5.84 \pm 1.42	36.91 \pm 5.89
	3 weeks of treatment	12.21 \pm 1.46	4.29 \pm 1.18	31.23 \pm 5.07*
t		0.243	1.623	4.833
P		0.809	0.109	0.000

Note: compared with those before treatment in the group, $P < 0.05$.

Table 3. Comparison of liver function change before and after treatment ($\bar{x} \pm sd$ U/L)

Grouping	ALT		AST	
	Before treatment	3 weeks of treatment	Before treatment	3 weeks of treatment
Observation group (n = 39)	28.99 \pm 9.86	38.79 \pm 12.13	18.64 \pm 7.62	21.49 \pm 10.37
Control group (n = 40)	29.34 \pm 8.79	35.34 \pm 11.76	19.34 \pm 6.98	21.43 \pm 11.05
t	0.167	1.284	0.426	0.025
P	0.868	0.203	0.671	0.980

Table 4. Comparison of renal function changes before and after treatment ($\bar{x} \pm sd$)

Grouping	BUN (mmol/L)		Cr (umol/L)	
	Before treatment	3 weeks of treatment	Before treatment	3 weeks of treatment
Observation group (n = 39)	5.13 \pm 1.96	6.78 \pm 1.53	59.13 \pm 10.38	61.05 \pm 11.42
Control group (n = 40)	5.11 \pm 2.03	6.89 \pm 1.64	60.33 \pm 10.45	62.45 \pm 10.95
t	0.045	0.308	0.512	0.556
P	0.965	0.759	0.610	0.580

Comparison of renal function between two groups

The BUN and Cr index levels before treatment in two groups were not significantly different ($P > 0.05$). After 3 weeks of treatment, the BUN and Cr levels of the OG and the CG increased ($P > 0.05$), and those of the OG after 3 weeks of treatment were not significantly different from the CG ($P > 0.05$) (Table 4).

Comparison of blood indices between two groups

The WBC level of the OG before treatment was $(2.58 \pm 1.12) \times 10^9/L$, after 1 week of treatment was $(5.89 \pm 1.54) \times 10^9/L$, and after 3 weeks of treatment was $(11.49 \pm 2.37) \times 10^9/L$; While the corresponding values in CG was $(2.61 \pm 1.03) \times 10^9/L$, $(1.59 \pm 1.01) \times 10^9/L$, and $(3.16 \pm 1.08) \times 10^9/L$.

The RBC level of the OG before treatment was $(2.89 \pm 0.34) \times 10^{12}/L$, after 1 week of treat-

ment was $(2.73 \pm 0.36) \times 10^{12}/L$, and after 3 weeks of treatment was $(2.85 \pm 0.46) \times 10^{12}/L$; while in the CG, the test results were $(2.90 \pm 0.79) \times 10^{12}/L$, $(2.99 \pm 0.65) \times 10^{12}/L$, and $(2.97 \pm 0.51) \times 10^{12}/L$.

The PLT levels of the OG before treatment, after 1 and 3 weeks of treatment were $(74.75 \pm 10.34) \times 10^9/L$, $(39.05 \pm 12.46) \times 10^9/L$, and $(67.85 \pm 15.49) \times 10^9/L$; As for the CG, they were $(76.95 \pm 12.43) \times 10^9/L$, $(24.49 \pm 10.47) \times 10^9/L$, and $(57.61 \pm 12.75) \times 10^9/L$.

In the OG, the Hb levels before treatment, after 1 and weeks of treatment were 83.66 ± 12.43 g/L, 81.49 ± 10.31 g/L, and 81.79 ± 12.46 g/L; In the CG, they were 83.66 ± 15.46 g/L, 92.43 ± 12.59 g/L and 88.31 ± 13.69 g/L.

The WBC, PLT levels of the OG after treatment were significantly higher ($P < 0.05$) and Hb levels after 1 week of treatment were significantly lower than those of the CG ($P < 0.05$) (Figures 2-5).

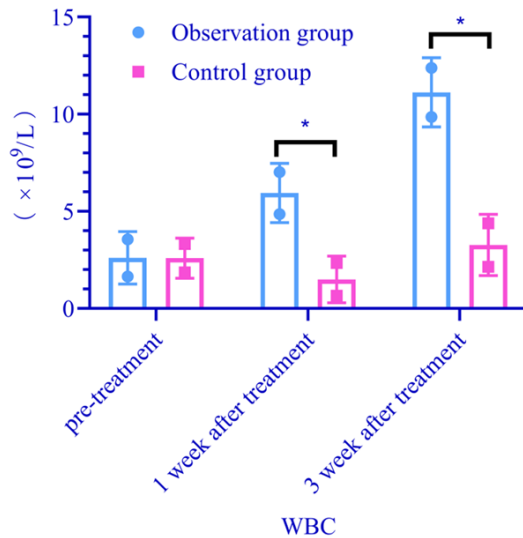


Figure 2. WBC level comparison. There was no significant difference in the WBC between the two groups before treatment ($P>0.05$). After 1 week and 3 weeks of treatment, the WBC levels of the OG were significantly higher than those of the CG ($P<0.05$). * indicates $P<0.05$ for comparison between the two groups.

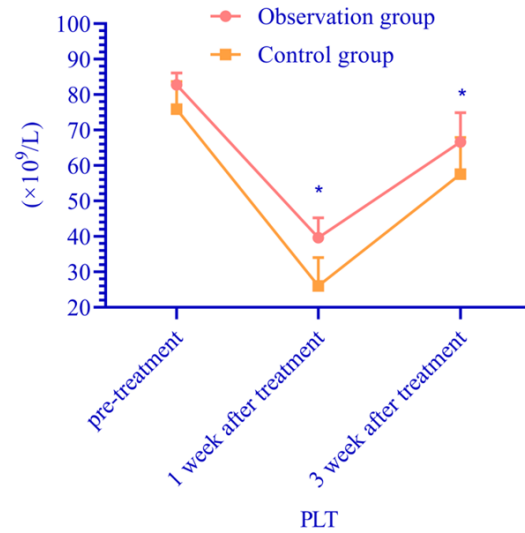


Figure 4. Comparison of PLT levels between two groups. There was no significant difference in PLT levels between the two groups before treatment ($P>0.05$). After 1 week and 3 weeks of treatment, the PLT levels of the OG were significantly higher than those of the CG ($P<0.05$). * indicates $P<0.05$ for comparison between the two groups.

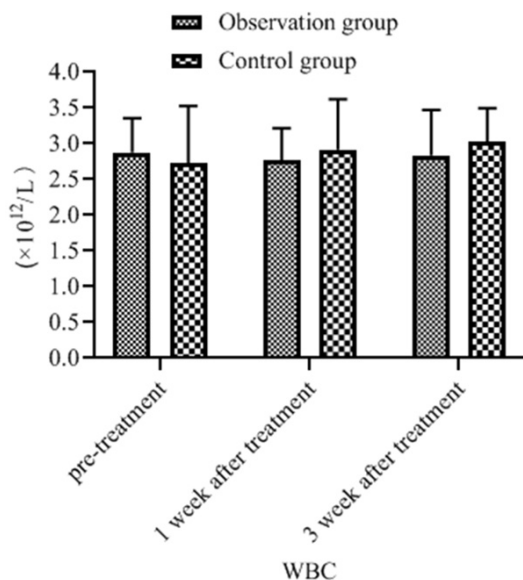


Figure 3. Comparison of the red blood cell count between two groups. There was no significant difference in RBC counts between the two groups before treatment and after 1 week and 3 weeks of treatment ($P>0.05$).

Discussion

Studies have shown that viruses, ionizing radiation, chemicals, genetics, innate factors, etc. are all risk factors for leukemia [7, 8]. Leukemia

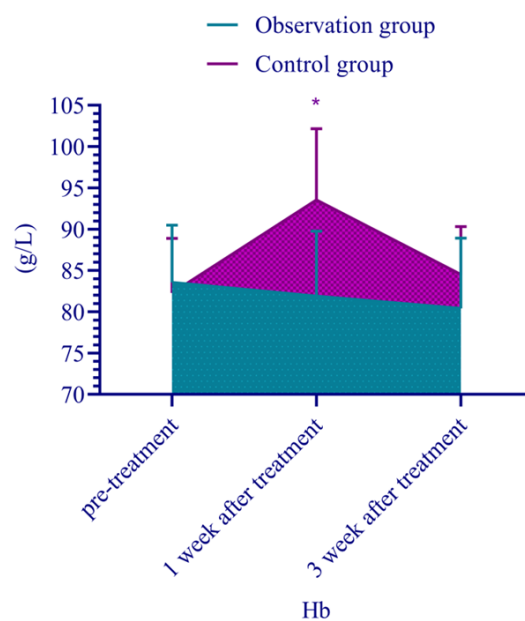


Figure 5. Comparison of hemoglobin levels between two groups. There was no significant difference in Hb levels between the two groups before treatment and 3 weeks after treatment ($P>0.05$). After 1 week of treatment, the Hb level of the OG was significantly lower than that of the CG ($P<0.05$). * indicates $P<0.05$ for comparison between the two groups.

has a very complicated pathogenesis not yet been fully elucidated, but it is generally believed

that inactivation of tumor suppressor genes, gene mutation and activation, and chromosome abnormalities contribute to the development of leukemia [9, 10]. Clinical manifestations of leukemia include hepatosplenic lymphadenopathy, fever, anemia, and bleeding [11]. For acute leukemia, chemotherapy is the main treatment option, covering remission induction therapy and post-remission therapy, prolonging the survival time of patients and improving their quality of life [12].

Hu et al [13] compared the application value of HAA and DA regimens, and showed that the incidence of grade III to IV bone marrow suppression after HAA regimen exceeded 20%, but was significantly lower than 45% of DA regimen. Newman et al [14] studied the application of IAG and IA chemotherapy in elderly leukemia patients, showing that the white blood cells, platelets, and hemoglobin and incidence of grade IV bone marrow suppression in the former group were significantly lower. Mapp et al's study on elderly leukemia patients revealed that patients receiving chemotherapy exhibit longer survival time than those receiving supportive treatment [15]. Although chemotherapy can effectively relieve the clinical symptoms, however, long-term chemotherapy can cause a variety of side effects which patients may not tolerate, and it is easy to cause bone marrow suppression, which seriously affects the safety of treatment [16]. In this study, in order to further improve the treatment effect and ensure the safety of treatment, the patients were treated with traditional Chinese medicine after chemotherapy.

This study showed that the OG was treated with traditional Chinese medicine after chemotherapy, and the patient's symptom indices were lower than the CG after treatment ($P < 0.05$). After 3 weeks, the APTT level was significantly higher than that of the CG ($P < 0.05$). The PLT level, WBC level of the OG after 1 week and 3 weeks of treatment was significantly higher than that of the CG ($P < 0.05$) while the Hb level was significantly lower than that of the CG after 1 week of treatment ($P < 0.05$). In addition, the liver and kidney functions of two groups did not differ significantly before and after treatment. These results suggested that traditional Chinese medicine can relieve the post-chemotherapy symptoms of acute leukemia patients

more quickly, and the blood coagulation function, the platelet count, white blood cell count, and hemoglobin level can be significantly improved, indicating that YYD can reduce the bone marrow suppression after chemotherapy, help to ensure the effect of chemotherapy and improve the safety of treatment. Zhu et al suggested that early intervention with spleen/stomach-strengthening, qi-replenishing and blood-arresting therapies after chemotherapy can speed up the recovery of spleen and stomach function and reduce the risk of infection [17]. Additional tonifying kidney therapy helps improve bone marrow suppression. Chang et al studied the treatment of acute leukemia patients with Fuzheng Anti-Tumor Decoction after chemotherapy [18], indicating that onset time of myelosuppression after chemotherapy was significantly shorter than that of the CG without traditional Chinese medicine (TCM) treatment, and the patients developed myelosuppression recovered more quickly than counterparts of the CG ($P < 0.05$).

According to clinical manifestations, leukemia can be categorized as fever and consumptive disease in TCM. Myelosuppression after chemotherapy will weaken the body's immune function, and the risk of anemia, bleeding, and infection is significantly increased [19]. In severe cases, it may directly threaten the life of patients. TCM also believes that acute leukemia originated from evil poison and yin and yin deficiency. Thus heat-clearing and detoxification, benefiting qi and nourishing yin should be the focus of therapies [20]. In this study, Astragalus and coastal glehnia root taste bitter, both of which are beneficial to lung Qi. Modern research LAO shows that *Ophiopogon japonicus* extracts can improve insulin resistance, and asparagus can play an immunoregulatory role. Cisplatin combined with those herbs can help strengthen the body's immune response and reduce possible adverse reactions caused by cisplatin [21]. Wang et al have shown that polysaccharides from *Saposhnikovia divaricate* can reduce serum IL-6 and TNF- α levels and increase TGF- β 1, NO, NOS levels in ovariectomized mice, improving osteoporosis [22]. *Atractylodes macrophylla* expels anemofrigid damp arthralgia; *Schisandra* benefits qi and strengthens yin and essence. Fu et al have demonstrated that schisandrin can reduce the survival rate of liver cancer cells (HCCLM3) and

can promote apoptosis of HCCLM3 cells [23]. Fleischer and others have shown that *Atractylodes macrocephala* decoction can improve the levels of IL-2 and IL-10 in rats with ulcerative colitis [24]. Shen et al found that *Atractylodes macrocephala* polysaccharide can up-regulate the cyt level of cells (Ca²⁺) and increase E-cadherin protein concentration [25].

In summary, YYD can benefit the symptoms quickly, improve the patient's blood coagulation function, and increase the platelets and WBC levels. It will not significantly affect the liver and renal function of the patients, has few adverse reactions and high safety, and thus has good application value. However, this study is a retrospective study, and the screening of subjects cannot be carried out in advance. Therefore, the results obtained are not sufficiently representative. In-depth research on a larger sample size should be conducted to obtain more representative conclusions and provide more guidance for the treatment of patients with acute leukemia after chemotherapy.

Disclosure of conflict of interest

None.

Address correspondence to: Sheng Wang, Department of Laboratory, Linzi District People's Hospital, No. 139 Huangong Road, Linzi District, Zibo, Shandong, China. Tel: +86-0533-7181189; +86-17660292317; E-mail: wangsssh5@163.com

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