Original Article
A comparison of the therapeutic, toxic, and side effects of cytarabine combined with different doses of idarubicin in the treatment of children with acute myeloid leukemia

Jingzhen Liu*, Yirong Ge*, Jiangwei Xu, Gangzuo Wang, Mei Rao, Jing Bi, Fang Wang, Yanbi Li

*Department of Pediatrics, Hubei Enshi Tujia and Miao Autonomous Prefecture Central Hospital, Enshi, Hubei, China. *Equal contributors and co-first authors.*

Abstract: Objective: This study aimed to compare the therapeutic, toxic, and side effects of cytarabine combined with different doses of idarubicin in the treatment of children with acute myeloid leukemia. Methods: 100 children with acute myeloid leukemia who were admitted to our hospital were selected as the study cohort and divided into a low-dose group, including 33 patients, a standard-dose group (the criteria group), including 34 patients, and a high-dose group, including 33 patients, according to the random number table method so as to compare the treatment's therapeutic, toxic, and side effects in these three groups. The three groups were all treated with 100 mg/m² cytarabine, based on which the low-dose group received 8 mg/(m²·d) idarubicin, the criteria group received 10 mg/(m²·d) idarubicin, and the high-dose group received 12 mg/(m²·d) idarubicin. Results: The OR rates of the high-dose and criteria groups were higher than the low-dose group's rate ($P<0.05$) and there were no statistical differences between the high-dose and criteria groups ($P>0.05$). The hemoglobin, platelets, and white cells were reduced after treatment in the three groups. The hemoglobin, platelets, and white cells of the low-dose and criteria groups were higher than they were in the high-dose group ($P<0.05$), and there were no statistical differences between the low-dose and criteria groups ($P>0.05$). The CD_3^+ and CD_4^+ levels were reduced, and the CD_8^+ level was increased after treatment in the three groups. The CD_3^+ and CD_4^+ levels in the low-dose and criteria groups were higher than they were in the high-dose group ($P<0.05$). The CD_8^+ levels in the low-dose and criteria groups were lower than they were in the high-dose group ($P<0.05$), and there were no statistical differences between the low-dose and criteria groups ($P<0.05$). After treatment, the Fbg and D-D serum levels increased and the TT was shortened in the three groups ($P<0.05$), but there were no statistical differences among the three groups ($P>0.05$). There was no statistical difference in the incidence of neutrophil deficiency among the three groups ($P>0.05$). There was a statistical difference in the incidence of neurotoxicity, gastrointestinal reactions, liver function damage, renal function damage, alopecia, and oral ulcers among the three groups ($P<0.05$). Conclusion: Cytarabine combined with a standard dose (10 mg/(m²·d)) of idarubicin can achieve a better therapeutic effect in the treatment of children with acute myeloid leukemia and improve the coagulation and fibrinolysis indexes in children, showing less hematotoxicity and immunosuppression and fewer toxic side effects, so it is worthy of promotion.

Keywords: Children, acute myeloid leukemia, cytarabine, idarubicin, toxic and side effect

Introduction

Acute myeloid leukemia in children is a common childhood blood disease, and its incidence accounts for approximately 30% of the acute leukemia cases in children [1]. With the development of medical technology, there is an increasingly high survival rate of children with acute myeloid leukemia, but the death and recurrence rates are still high. According to one study, the 5-year, event-free survival of this disease is about 50%-60% [2]. Now, the main induction therapy of acute myeloid leukemia in children is cytarabine combined with anthracyclines, of which idarubicin is a common anthracycline. As for acute myeloid leukemia patients below 60 years old, the recommended dose of idarubicin is 12 mg/(m²·d) according to the

National Comprehensive Cancer Network and 8-10 mg/(m^2·d) in China [3]. Relevant foreign studies have shown that in the treatment of untreated acute myeloid leukemia with idarubicin plus cytarabine (IA protocol), the dose of idarubicin was 12 mg/(m^2·d), and the complete response rate (the CR rate) was 80%, which is higher than daunorubicin plus cytarabine (the DA protocol) (CR rate 58%) [4] Domestic studies have shown that after one course of treatment in the high standard-dose group (10-12 mg·m^{-2}·d^{-1}), the low standard-dose group (8-9 mg·m^{-2}·d^{-1}), and the low-dose group (<8 mg·m^{-2}·d^{-1}), the CR rates were 79.4%, 75.5%, and 46.8% respectively [5]. It can be seen that the high standard-dose and the low standard-dose of idarubicin have certain advantages over the low-dose of idarubicin and daunorubicin in the treatment of acute myeloid leukemia. However, at present, there are no studies on the treatment of children with acute myeloid leukemia using cytarabine combined with different doses of idarubicin. This paper aimed to observe the therapeutic, toxic, and side effects of cytarabine combined with 8 mg/(m^2·d), 10 mg/(m^2·d), or 12 mg/(m^2·d) idarubicin in the treatment of children with acute myeloid leukemia and the influence on the blood routine, immune function and coagulation and fibrinolysis indexes. The report is given below.

Material and methods

General data

100 children with acute myeloid leukemia who were admitted to our hospital from January, 2014 to January, 2016 were selected as the study cohort and divided into a low-dose group, including 33 patients, a standard-dose group (the criteria group), including 34 patients, and a high-dose group, including 33 patients, according to the random number table method. Inclusion criteria: This study included (1) patients who were newly-diagnosed children; (2) those who were diagnosed through pathology; (3) those aged 1-13 years old; and (4) those whose family members signed the letter of consent. Exclusion criteria: This study excluded (1) patients complicated with malignant tumors; (2) those complicated with other hematological system diseases; (3) those complicated with autoimmune or metabolic diseases; (4) those complicated with congenital malformations; (5) those complicated with congenital

heart disease; (6) those with severe malnutrition; (7) those with hepatic and renal insufficiency; and (8) those complicated with severe infections.

Methods

The three groups were injected with 100 mg/m^2 cytarabine (Sinopharm A-THINK Pharmaceutical Co. Ltd., SFDA approval number: H20055127) through an intravenous drip every 12 hours for 7 consecutive days. On this basis, the low-dose group was injected with 8 mg/(m^2·d) idarubicin (Pfizer Pharmaceuticals Limited, SFDA approval number: H20040600) through an intravenous drip from the first to the third days; the criteria group was injected with 10 mg/(m^2·d) idarubicin through an intravenous drip from the first to the third days; and the high-dose group was injected with 12 mg/(m^2·d) idarubicin through an intravenous drip from the first to the third days. After all the patients were treated with the first course, those in complete remission continued to receive the same therapy for the consolidation treatment.

Evaluation criteria

(1) Evaluation of the therapeutic effect: Complete remission (CR): The symptoms and signs of leukemia disappeared completely, with hemoglobin ≥100×10^9/L and neutrophil > 1.5×10^9/L. Partial remission (PR): The symptoms and signs of leukemia were improved, with the bone marrow blast cells + the juvenile cells accounting for 6%-20%. Non-remission (NR): The symptoms and signs of leukemia were not apparently improved, with the bone marrow blast cells + juvenile cells >20%. Overall response (OR) rate = CR%+PR%. (2) Blood routine: 3 ml peripheral venous blood was collected before treatment and at 3 days after treatment to determine the hemoglobin, platelet, and white cell levels using a MEK-7222K hematology analyzer manufactured by Nihon Kohden. (3) Immune function: 2 ml peripheral venous blood was collected before treatment and at 3 days after treatment and put into an anticoagulation tube. Then, the direct immunofluorescence staining method was used to mark the monoclonal antibodies and a Beckman Coulter Flow Cytometer manufactured by Becton, Dickinson and Company was used to determine the immune function indexes, i.e. CD_3^+, CD_4^+ and CD_8^+. (4) Fibrinogen (Fbg), D-Dimer, (D-D),

Table 1. Comparison of the general data among the three groups ($\bar{x} \pm s$, n)

Group	n	Gender		Average age (years old)	Disease type						Disease severity		
		Male	Female		M2	M3	M4	M5	M6	M7	Low risk	Moderate risk	High risk
Low-dose group	33	18	15	6.51±1.03	7	12	6	7	0	1	3	18	11
Criteria group	34	20	14	6.42±1.25	8	10	7	7	1	1	4	20	9
High-dose group	33	19	14	6.34±1.15	9	10	6	5	2	1	4	17	12
χ^2/t		0.132		0.217			0.165					0.849	
P		0.936		0.830			0.912					0.232	

Table 2. Comparison of the therapeutic effect among three groups [n (%)]

Group	n	CR	PR	NR	OR
Low-dose group	33	14 (42.42)	6 (18.18)	13 (39.39)	20 (60.61)
Criteria group	34	26 (76.47)	6 (17.65)	2 (5.88)	32 (94.12)
High-dose group	33	27 (81.82)	5 (15.15)	1 (3.03)	32 (96.97)
χ^2		-	-	-	20.158
P		-	-	-	0.000

and thrombin time (TT): 3 ml peripheral venous blood was collected before treatment and at 3 days after treatment for centrifugation at 3,000 r/min for 10 minutes. The coagulation method was used to measure the Fbg and TT, and immunoturbidimetry was used to measure the D-D. The detecting instrument was a CA7000 automated coagulation analyzer manufactured by Sysmex Corporation. (5) The incidences of the toxic and side effects were observed.

Statistical analysis

SPSS 25.0 statistical software was used for the analysis. The measurement data was represented using $\bar{x} \pm s$ in a t test; and the enumeration data was represented by % in a χ^2 test. $P<0.05$ meant that there was a statistical significance.

Results

Clinical data

There were no statistical differences, but comparability, in terms of gender, age, disease type, and disease severity among the three groups ($P>0.05$), as shown in **Table 1**.

Comparison of the therapeutic effect among the three groups

The OR rates of the high-dose and criteria groups were higher than they were in the low-

dose group ($P<0.05$), and there was no statistical difference between the high-dose and criteria groups ($P>0.05$), as shown in **Table 2**.
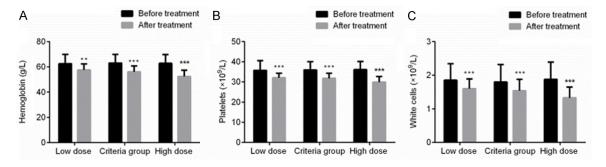
Comparison of the blood routine among the three groups

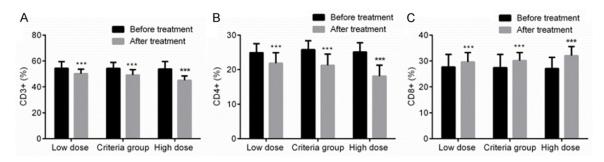Before treatment, there were no statistical differences in the hemoglobin, platelet, and white cell levels among three groups ($P>0.05$). After treatment, the hemoglobin, platelet, and white cell levels were reduced in the three groups. The hemoglobin, platelet, and white cell levels in the low-dose and criteria groups were higher than they were in the high-dose group ($P<0.05$), and there was no statistical difference between the low-dose and criteria groups ($P>0.05$). This implies that cytarabine combined with a large dose of idarubicin had a more apparent effect on myelosuppression, and the hemoglobin, platelets, and white cells were slightly reduced in the low-dose and criteria groups, as shown in **Figure 1**.
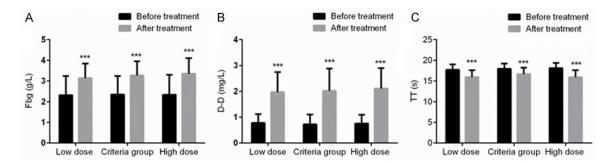
Comparison of immune function among three groups

Before treatment, there were no statistical differences in the CD_3^+, CD_4^+, and CD_8^+ levels among the three groups ($P>0.05$). The CD_3^+ and CD_4^+ levels were reduced, and the CD_8^+ level was increased after treatment in three groups. The CD_3^+ and CD_4^+ levels in the low-dose and criteria groups were higher than they were in the high-dose group ($P<0.05$); the CD_8^+ levels in the low-dose and criteria groups were lower than they were in the high-dose group ($P<0.05$), and there was no statistical difference between the low-dose and criteria groups ($P<0.05$). This implies that cytarabine combined with different

Figure 1. Comparison of the blood routine among three groups ($\bar{x} \pm s$). A. For hemoglobin; B. For platelets; C. For white cells. Note: Compared with that the levels before treatment, ***$P<0.001$.

Figure 2. Comparison of the immune function among the three groups ($\bar{x} \pm s$, %). A. For CD_3^+; B. For CD_4^+; C. For CD_8^+. Note: Compared with that the levels before treatment, ***$P<0.001$.

Figure 3. Comparison of the coagulation function indexes among the three groups ($\bar{x} \pm s$, s). A. For Fbg; B. For D-D; C. For TT. Note: Compared with that the levels before treatment, ***$P<0.001$.

doses of idarubicin had an apparently inhibiting effect on cellular immune function, as shown in **Figure 2**.

Comparison of the coagulation function indexes among three groups

After treatment, the Fbg and D-D serum levels increased, and the TT was shortened in the three groups ($P<0.05$), but there were no statistical differences in the comparisons of the three groups ($P>0.05$), as shown in **Figure 3**.

Comparison of the toxic and side effects among the three groups

There was no statistical difference in the incidence of neutrophil deficiency among the three groups ($P>0.05$). There was a statistical difference in the incidence of neurotoxicity, gastrointestinal reaction, liver function damage, renal function damage, alopecia and oral ulcers among the three groups ($P<0.05$). This implies that a low dose or the standard dose of idarubi-

Table 3. Comparison of the toxic and side effects among three groups [n (%)]

Group	n	Neutrophil deficiency	Neurotoxicity	Gastrointestinal reaction	Liver function damage	Renal function damage	Alopecia	Oral ulcer
Low-dose group	33	100 (100.00)	1 (3.03)	25 (75.76)	1 (3.03)	1 (3.03)	8 (24.24)	2 (5.88)
Criteria group	34	100 (100.00)	3 (8.82)	28 (82.35)	2 (5.88)	3 (8.82)	10 (29.41)	2 (5.88)
High-dose group	33	100 (100.00)	9 (27.27)	33 (100.00)	7 (21.21)	8 (24.24)	21 (63.64)	9 (27.27)
X^2		0.000	9.209	8.678	7.031	7.523	12.754	8.872
P		1.000	0.010	0.013	0.030	0.023	0.002	0.012

cin is safer from the perspective of toxic and side effects, as shown in **Table 3**.

Discussion

Cytarabine combined with anthracyclines has a better therapeutic effect in the induction therapy of primary and untreated acute myeloid leukemia, and the complete remission rate is 60%-80% as reported [4-6]. Idarubicin is formed when methylol groups on the daunorubicin glycosyl are replaced by hydrogen atoms. As a new anthracycline, it is characterized by a strong lipid solubility and a long half-life period. Compared with daunorubicin, idarubicin has a larger intake of cells, a stronger anticancer effect, and less cardiotoxicity [7]. Cytarabine, a pyrimidine antimetabolite, is converted into cytarabine triphosphate after ingestion and plays a role in blocking the DNA synthetic pathway. It is not only a cell cycle specific agent in the S phase, but also a common drug for leukemia [8]. Also, cytarabine combined with idarubicin can achieve a synergistic effect. In this paper, the recommended minimum dose of 8 mg/(m²·d) was taken as the low dose of idarubicin, 10 mg/(m²·d) was taken as the standard dose, and 12 mg/(m²·d) as recommended in America was taken as the high dose for the comparisons. The results showed that the remission rates of the criteria and high-dose groups were higher than the rates in the low-dose group in induction therapy. Previous research [9, 10] indicated that cytarabine combined with a standard dose of idarubicin had a better therapeutic effect in comparison with cytarabine combined with a low dose of idarubicin. This indicates that the cytarabine combined with a standard dose or high dose of idarubicin can achieve a satisfactory effect in the induction therapy of acute myeloid leukemia in children.

Myelosuppression is a common toxic and side effect in induction therapy using cytarabine combined with anthracyclines, manifesting as a reduction of hemoglobin, platelets, and white cells. The infections and hemorrhages caused by myelosuppression are major causes of the reduction in the quality of life of children with acute myeloid leukemia [11, 12]. According to the study, induction therapy based on 10 mg/(m²·d) idarubicin combined with homoharringtonine and acarbose led to a 100% incidence of Grade IV hematotoxicity in the initial treatment of young patients with acute myeloid leukemia, and the rate of infection caused by agranulocytosis was as high as 70% [13]. In a study on the induction therapy of adult patients with acute myeloid leukemia, all the patients were able to achieve Grade IV myelosuppression after the adoption of 10 mg/(m²·d) idarubicin combined with acarbose, the rate of infection caused by myelosuppression was over 90%, and the platelets were as low as 2×10⁹/L [14]. As shown in this study, the hemoglobin, platelet, and white cell levels were reduced after treatment in the three groups and more apparently reduced in the high-dose group. It could be seen from this that cytarabine combined with a large dose of idarubicin has more obvious myelosuppression and the hemoglobin, platelet, and white cell, levels were reduced slightly in the low-dose and criteria groups, so the low and standard doses of idarubicin are safer, with a smaller influence on hematopoietic function.

Immune dysfunction is a vital reason for the occurrence and development of malignant tumors [15]. The T-cell subset has the functions of cellular immunity and immunoregulation. In addition, as an important part of antitumor immunity, the T-cell subset plays a central regulatory role in tumor immunity. Therefore, the CD_3^+ level reflects the total lymphocyte count;

CD_4^+ is the major responding cell, and CD_8^+ can recognize the endogenous antigen peptide T cells presented by MHCl molecules and has a cytotoxic effect that is mediated by cells on the target cells [16]. Relevant research shows that the T cell subset and the NK cells of young patients with acute myeloid leukemia are lower than those in the healthy control group, and the viability of the T cell subset and the NK cells were reduced for 2 weeks after chemotherapy in comparison with the levels before chemotherapy [17]. Meanwhile, recent studies indicate that CD_3^+ and CD_4^+ in children with acute myeloid leukemia are greatly reduced compared with normal children [18]. This study indicates that CD_3^+ and CD_4^+ are reduced and CD_8^+ is increased after treatment in the three groups, which is consistent with similar studies [19]. Therefore, the changes in the T cell subset in the high-dose group are more apparent than those in the low-dose and criteria groups. This implies that the cytarabine combined with different doses of idarubicin has a clear inhibiting effect on cellular immune function. Chemotherapy mainly aims to kill the leukemia cells in large quantities and ease the burdens caused by the tumor cells. The higher the dose of chemotherapeutic drugs used, the more the leukemia cells will be killed, and the greater the damage made to normal cells and the more apparent the immunosuppression achieved, simultaneously enhancing the remission rate. Hence, the in high-dose group, CD_3^+ and CD_4^+ were more apparently reduced, and the immunosuppression was more significant. So the low dose or standard dose of idarubicin was safer.

It was found in relevant studies that the indexes of coagulation/fibrinolysis are abnormal in children with acute myeloid leukemia to a different extent, and the TT is prolonged and D-D increased in children with acute myeloid leukemia compared with the normal children in control group [20]. The mechanism for the abnormal indexes of coagulation/fibrinolysis in acute myeloid leukemia patients is mainly due to a variety of tumor-related substances, such as tissue factors and cancer procoagulants that break the balance of coagulation, anticoagulation, and fibrinolysis in human body. Fbg is not only a blood coagulation factor, but it is also the substrate of thrombin and plasmin. TT refers to the time needed for the appearance of fibrinogen, and the extension of TT is mainly seen in

hypofibrinogenemia and the increase of fibrinogen degradation products, etc. D-D, as the degradation product of cross-linked fibrin, is an important index used to determine coagulation. Relevant studies [21] showed that TT was shortened and Fbg and D-D increased in leukemia patients after treatment with daunorubicin or idarubicin combined with cytarabine and the drug induction of aclacinomycin, etc. And there was no obvious change in prothrombin time and activated partial thromboplastin time. It was found in this study that Fbg and D-D in serum were increased, and TT was shortened after treatment in the three groups, but the differences among the groups were not obvious, which is consistent with the findings of previous studies [22]. This indicates that chemotherapy could affect the coagulation function and fibrinolytic system of children with acute myeloid leukemia. Its mechanism may involve a large amount of prolamins and tryptases, etc. in the blood of children with acute myeloid leukemia, which can decrease the blood coagulation factors or reduce the haemostatic activity. At the same time, the leukemia cells can synthesize a large amount of anticoagulants to break the balance of coagulation, anticoagulation, and fibrinolysis in the human body. Furthermore, leukemia cells can also cause liver damage and thus affect the function of the liver to induce and generate blood coagulation factors, which will decrease the blood coagulation factors or reduce the hemostatic activity [23, 24]. Chemotherapeutic drugs can kill the leukemia cells in large quantities to activate the fibrinolytic system and keep a hypercoagulable state in child patients.

There was no statistical difference in the incidence of neutrophil deficiency in terms of its toxic and side effects, which indicated that idarubicin of 8-12 mg/(m²·d) can lead to severe hematotoxicity. There was a statistical difference in the incidence of neurotoxicity, gastrointestinal reactions, liver function damage, renal function damage, alopecia, and oral ulcers among the three groups, which implies that the incidence of toxic and side effects, such as neurotoxicity and gastrointestinal reactions, etc., increased with the increasingly high dose of idarubicin. Therefore, the low or standard doses of idarubicin are safer from the perspective of the toxic and side effects.

In conclusion, cytarabine combined with a standard dose (10 mg/(m²·d)) of idarubicin can achieve a better therapeutic effect in the treatment of children with acute myeloid leukemia, with less myelosuppression, immunosuppression, and toxic and side effects, so it is worthy of promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Yanbi Li, Department of Pediatrics, Hubei Enshi Tujia and Miao Autonomous Prefecture Central Hospital, No. 158, Wuyang Avenue, Enshi Prefecture, Hubei, China. Tel: +86-0718-8295503; E-mail: k87664x4@163.com

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