Original Article
Short- and long-term survival analysis of IDA at 3 doses combined with Ara-C in treating newly diagnosed pediatric AML

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Abstract: Objective: This study was designed to compare the effects of Idarubicin (IDA) at two doses on newly diagnosed AML when combined with Ara-C. Methods: A total of 99 newly diagnosed AML patients between January and December 2014 were evenly randomized into the low-dose group [n=33, IDA 3 mg/(m^2·d) + Ara-C 100 mg/(m^2·d)], the medium dose group [n=33, IDA 10 mg/(m^2·d) + Ara-C 100 mg (m^2·d)], and the high-dose group [n=33, IDA 15 mg/(m^2·d) + Ara-C 100 mg/(m^2·d)] by a Random Number Method. Short-term efficacy, side effects, 3-year survival rate and reoccurrence were compared between the three groups. Results: The overall response rate (ORR) was 27.27% in the low-dose group, 54.55% in the medium dose group, and 60.61% in the high-dose group, showing a significant difference between the groups (P<0.05). The incidence of side effects was 36.36% in the low-dose group, 39.39% in the medium dose group and 69.70 in the high-dose group, showing a significant difference between the groups (P<0.05). The 3-year survival rate of the medium dose group and the high-dose group was higher than that of the low-dose group (P<0.05), but there was no significant difference between the medium dose group and the high-dose group (P>0.05). Conclusion: For newly diagnosed AML patients, the combination of IDA at 10 mg/m^2 and Ara-C could significantly enhance the short-term efficacy, the short- and long-term survival rate with few side effects.

Keywords: IDA, Ara-C, AML, survival rate

Introduction

Leukemia is a clonal malignant disease associated with abnormal hematopoietic stem cells. According to the maturity of leukemia cells and its natural course, the disease is divided into acute and chronic types, in the clinic. Acute leukemia is further broken down into acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). As recorded, AML accounts for 20% of the acute leukemia and more than 50% of the deaths. It has been identified as a focus in the study of pediatric blood diseases for its refractoriness [1, 2].

In recent years, though therapies such as risk stratification, immunotherapy and stem cell transplantation are continuously improving the efficacy and prognosis of pediatric AML, the 5-year survival rate ranges only between 49% and 63%, far lower than that of the ALL, which is 76%~86% [3, 4]. As an anthracycline antitu-

mor drug and a daunorubicin analogue, IDA structurally differs from daunorubicin by removal of a methoxy group at glycoside C4, which allows it to be highly fat soluble for cell absorption to thoroughly kill cancer cells. For over 4 decades Ara-Czhiliao has been applied in treating leukemia, especially ANLL, with clinical remission rates between 60% and 80%. The "3 + 7" regimen (IDA + Ara-C) has been incorporated into the AML Guidance 2009-2010 issued by the National Comprehensive Cancer Network (NCCN) [5]. Tp further improve the clinical efficacy, studies have been conducted to analyze the effects of IDA and Ara-C combination at various doses.

At the present stage, most of the studies on IDA + Ara-C are in relation to adult AML patients rather than children. Disputes always exist in the IDA dose. This study explored the efficacy and effects of IDA at three doses on the quality of life of newly diagnosed AML children when

combined with Ara-C at routine doses for more reliable future guidance.

Materials and methods

Materials

A total of 99 AML patients admitted to our hospital between January and December 2014 were randomized into the low-dose group, (n= 33), medium dose group (n=33), and the high-dose group (n=33) by a Random Number Method. The 33 patients in the low-dose group consisted of 20 males and 13 females. Eight were categorized as M_0, 7 as M_2, 9 as M_4 and 9 as M_5 according to FAB typing. In the medium dose group, there were 19 males and 14 females; the number of patients grouped as M_0, M_2, M_4 and M_6 were respectively 8, 6, 11 and 8. In the high-dose group, there were 19 males and 14 females; the number of patients grouped as M_0, M_2, M_4 and M_6 were respectively 7, 7, 10 and 9. This study was approved by the Ethics Committee of the Yinzhou People's Hospital.

Inclusion and exclusion criteria

Inclusion criteria: ① Diagnosed with AML through histochemical staining and bone marrow morphology according to the *Diagnosis and Treatment-Related Complications of Acute Leukemia: An Evidence-Based Guide* [6]; ② No abnormality in organ functions or severe complications; ③ Good treatment adherence; ④ Informed consent from the patient or his/her family members. Exclusion criteria: ① Congenital disease; ② Dysfunctions and metabolic diseases in liver and kidney; ③ Acute leukemia from myelodysplastic syndrome; ④ Involvement in other clinical studies.

Methods

IA regimen-induced chemotherapy was applied in the three groups. The low-dose group was treated with IDA 3 mg/(m²·d) (once daily, from d1-3), combined with Ara-C 100 mg/(m²·d) (once daily, from d1-7). The medium dose group was treated with IDA 10 mg/(m²·d) (once daily, from d1-3), combined with Ara-C 100 mg/(m²·d) (once daily, from d1-7). The high-dose group was treated with IDA 15 mg/(m²·d) (once daily, from d1-3), combined with Ara-C 100 mg/(m²·d) (once daily, from d1-7). After 3 to 4 weeks (one course) of chemotherapy, bone marrow aspiration was performed to evaluate the efficacy. For complete response (CR) patients, the original regimen was used for one to two courses for reinforcement, followed by Ara-C at 150 mg/m². For partial response (PR) patients, the original regimen was continued. For stable disease (SD) and progressive disease (PD) patients, a new regimen was applied.

Observation indices

(1) Efficacy judgment criteria: efficacy was evaluated after one course, referring to the efficacy evaluation criteria [7]. CR: no signs and symptoms as a result of leukemia cell infiltration, QOL recovering to or approaching normal level; Absolute Neutrophil Count $\geq 1.5 \times 10^9$/L, hemoglobin >90 g/L, platelet count $\geq 100 \times 10^9$/L; no leukemia cells according to the categorization of general white cells in the peripheral blood, the number of primitive and juvenile lymphocytes in myelogram under 5%, megacaryocytes and red blood cells. PR: the number of myelogram primitive and juvenile lymphocytes account for 5%-20%; or hemogram, clinical signs/symptoms not yet reaching the criteria of CR. Reoccurrence: ① The number of myelogram primitive and juvenile lymphocytes between 5% and 20%, but not reaching the criteria of CR after one course. ② The number of primitive and juvenile lymphocytes over 20%. ③ Extramedullary leukemia cell infiltration. Reoccurrence is established in any of the 3 cases for patients judged as CR after treatment.

(2) Adverse reactions: the three groups were recorded for the incidences of bone marrow arrest, lipsotrichia, infection and dental ulcers during chemotherapy.

(3) QOL: QOL was scored between 0 and 100 from perspectives of schooling at the school age, time of playing with companions, average increase in height, acute respiratory infection, adolesce and medical burdens on the family. The final score is negatively associated with the patients' QOL.

(4) Psychological evaluation: the self-rating anxiety scale (SAS) and self-rating depression scale (SDS) were adopted to evaluate the psychological status of the three groups before, at 1 month, 6 months and 12 months after chemotherapy. With 50 as the boundary, anxiety/

Table 1. Comparison of general clinical data among the three groups ($\bar{x} \pm s$)/[n/(%)]

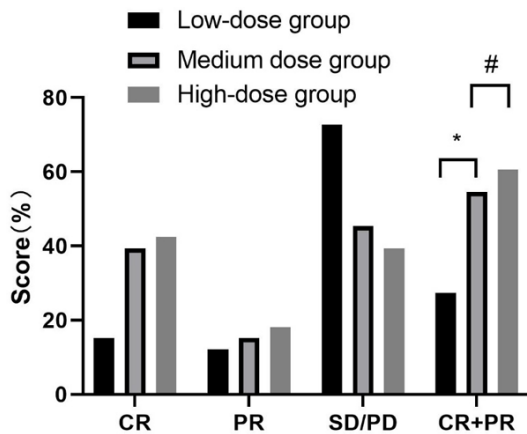| General clinical data		Low-dose group (n=33)	Medium dose group (n=33)	High-dose group (n=33)	t/X^2	P
Gender	Male	20	19	19	0.27	0.603
	Female	13	14	14		
Average age (years)		8.21±0.32	8.19±0.41	8.32±0.33	0.157	0.876
Average BMI (kg/m^2)		18.18±1.29	18.21±1.21	18.31±1.09	0.062	0.951
FAB classification	M_0	8	8	7	0.312	0.567
	M_2	7	6	7		
	M_4	9	11	10		
	M_5	9	8	9		

Figure 1. Intergroup comparison of efficacy. The number of CR, PR and SD/PD patients, and the ORR were 5, 4, 24 and 27.27% in the low-dose group, 13, 5, 15 and 54.55% in the medium dose group, and 14, 6, 13 and 60.61% in the high-dose group. Compared between groups, ORR in the medium dose and high-dose groups were significantly higher than that in the low-dose group (P<0.05), but there was no significant difference between the medium dose and high-dose groups, * indicates that the difference between the groups was statistically significant (P<0.05), while # indicates that the difference between the groups was not statistically significant (P>0.05).

depression is graded at three levels, i.e., mild (50-59), moderate (60-69) and severe (>70) [8, 9].

(5) Short- and long-term survival rates: survival rates between 1-3 years after treatment were used to draw a Kaplan-Meier curve to analyze the patients' short- and long-term survival rates.

Statistical analysis

Statistical analysis was performed with SPSS 22.0. In case of nominal data expressed as %, comparison studies were carried out through chi-squared test for intergroup comparison. In case of numerical data expressed as $\bar{x} \pm s$, comparison studies were carried out through independent-samples T test for data which were normally distributed. Data were analyzed by the Kaplan-Meier method, and tested by the Log-rank method. For all statistical comparisons, significance was defined as P<0.05.

Results

General clinical data

There were no statistically significant differences between patients in the three groups in general clinical data such as gender, age, average course of disease, and FAB classification (P> 0.05), which were comparable (**Table 1**).

Intergroup comparison of efficacy

After treatment, there were 5 cases of CR, 4 cases of PR, and 24 cases of SD/PD in the low-dose group, with ORR of 27.27%. The medium dose group had 13 cases of CR, 5 cases of PR and 15 cases of SD/PD, with ORR of 54.55%. In the high-dose group, there were 14 cases of CR, 6 cases of PR, and 13 cases of SD/PD, with ORR rate of 60.61%. Intergroup comparison showed that the ORR of the medium dose group and the high-dose group was significantly higher than that of the low-dose group (P<0.05), but there was no significant difference between the medium dose group and the high-dose group (P>0.05) (**Figure 1** and **Table 2**).

Intergroup comparison of incidence of adverse reactions

The difference of adverse reactions showed that the total incidence of bone marrow sup-

Table 2. Intergroup comparison of clinical efficacy [n (%)]

Group	n	CR	PR	SD/PD	ORR
Low-dose group	33	5 (15.15)	4 (12.12)	24 (72.73)	9 (27.27)
Medium dose group	33	13 (39.39)	5 (15.15)	15 (45.45)	18 (54.55)*
High-dose group	33	14 (42.42)	6 (18.18)	13 (39.39)	20 (60.61)*,#
F	-	-	-	-	4.539
P	-	-	-	-	<0.001

Compared with the low-dose group, *P<0.05; compared with the medium dose group, #P>0.05.

Table 3. Incidences of adverse reactions during the chemotherapy [n (%)]

Adverse reaction	Low-dose group (n=33)	Medium dose group (n=33)	High-dose group (n=33)	F	P
Bone marrow suppression (III-IV)	2 (6.06)	3 (9.09)	5 (15.15)	-	-
Infection	1 (3.03)	3 (9.09)	4 (12.12)	-	-
Gastrointestinal reactions	2 (6.06)	3 (9.09)	3 (9.09)	-	-
Hair loss	1 (3.03)	1 (3.03)	2 (6.06)	-	-
Oral ulcer	3 (9.09)	3 (9.09)	4 (12.12)	-	-
Palpitation and oppression in chest	2 (6.06)	1 (3.03)	3 (9.09)	-	-
Others	1 (3.03)	1 (3.03)	2 (6.06)	-	-
Total incidence	12 (36.36)	13 (39.39)	23 (69.70)	4.33	<0.001

pression, infection, hair loss and oral ulcers was 36.36% in the low-dose group, 39.39% in the medium dose group, and 69.70% in the high-dose group. Intergroup comparison showed that the overall incidence of adverse reactions in the low-dose group and the medium-dose group was significantly lower than that in the high-dose group (P<0.05), but there was no significant difference between the low-dose group and the medium-dose group (P>0.05) (**Table 3**).

Intergroup comparison of short-term QOL after chemotherapy

At 1 week and 1 month after the chemotherapy, there was no significant difference in QOL scores among the three groups (P>0.05). At 6 months and 12 months after the chemotherapy, the QOL scores in the medium group were significantly higher than those in the low-dose and high-dose groups (P<0.05) (**Figure 2**).

Intergroup comparison of psychological scores

There was no significant difference in SAS and SDS scores among the three groups before chemotherapy (P>0.05). At 1 month, 6 months and 12 months after the chemotherapy, the SAS and SDS scores in the medium dose group were significantly lower than those in the high-dose and low-dose groups. At the same time, the SAS and SDS scores of patients in the medium dose group showed a significant downward trend over time, with significant differences between the groups (P<0.05) (**Figure 3**).

Intergroup comparison of short- and medium-term survival rates after chemotherapy

Follow-up showed that the 1-year survival rate, 2-year survival rate and 3-year survival rate were 78.79% (26/33), 39.39% (13/33), and 30.30% (10/33), respectively in the low-dose group. The 1-year survival rate, 2-year survival rate and 3-year survival rate were 81.82% (27/33), 75.76% (25/33), and 63.64% (21/33), respectively in the medium dose group. The 1-year survival rate, 2-year survival rate and 3-year survival rate were 78.79% (26/33), 69.70% (23/33), and 60.61% (20/33), respectively in the high-dose group. Intergroup comparison showed that the 1-year survival rate of the three groups was not significantly different (P>0.05). The 2-year survival rate of the medium dose and the high-dose groups was higher than that of the low-dose group (P<0.05), but there was no significant difference between the medium dose group and the high-dose group (P>0.05).
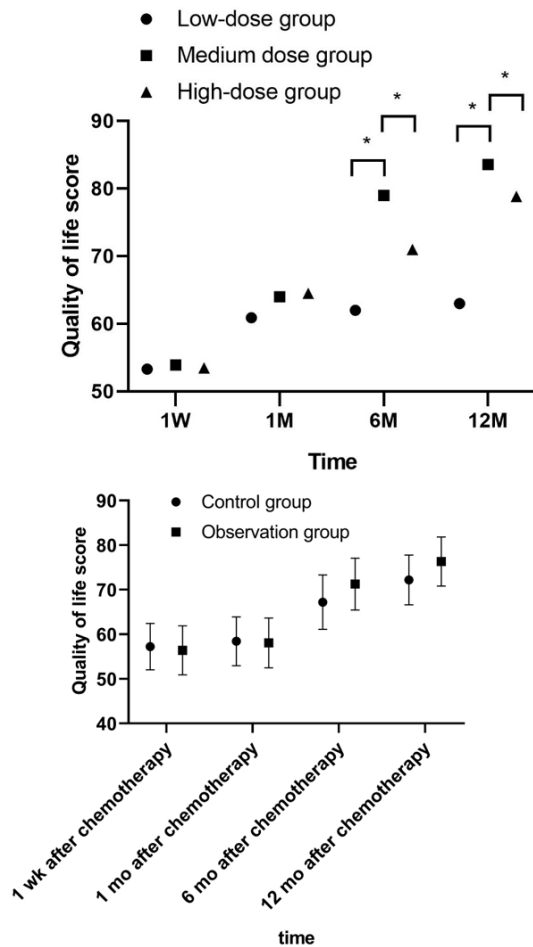
Figure 2. Changes in QOL scores after chemotherapy. At 1 week and 1 month of follow-up, there was no significant difference in the scores of patients' QOL among the three groups (P>0.05). At 6 months and 12 months of follow-up, QOL of patients in the medium dose group was significantly higher than that in the low-dose and the high-dose groups (P<0.05). * indicates that the difference between groups of the same indicator at the same time is statistically significant.

Discussion

Chemotherapy is the most important therapy for AML patients, and provides a basis for hematopoietic stem cell transplantation provided that patients' conditions are controlled. A standard chemotherapy regimen consists of 2 stages generally, remission and induction, and maintenance treatment. The former manages to control patients' conditions through combination with chemotherapy to kill cancer cells, while the latter is designed to reinforce the efficacy [10-12]. The rapid progression of AML demands a high dose of chemotherapy drugs,

which may lead to severe bone marrow arrest, mucosal injury and high risk of hospital infection. According to relevant studies, the hospital infection rate of AML is very close to numbers in the ICU and significantly higher than high-risk departments such as surgery and pediatrics. Infection prevention is a key to improve the efficacy of AML patients receiving chemotherapy [13, 14]. As a new anthracycline antitumor drug, IDA differs from daunorubicin at position C4 where the methoxy group is replaced by a H atom, in order to significantly raise the lipotropy to obtain high concentrations between cells and marrow cells through the cytomembrane; and therefore, reinforce the cell killing effects. Its major metabolite, IDA alkoxide, can also suppress the activity of tumors; with a half life between 41 and 69 h, IDA can damage the single chain DNA in tumor cells, and has shown antineoplasmic activity 5 times over Daunorubicin (DNR) according to *in vitro* cell experiments [8, 9]. IDA does not induce P glycoprotein expression and therefore is not susceptible to and is inferior in its resistance as compared with other anthracyclines [15]. Ara-C is a synthesized pyrimidine nucleotide, and Ara-CTP is an active substance capable of resisting tumors through the following 3 possible mechanisms: ① Ara-CTP is converted to NTP Ara-C to block the DNA synthesis by inhibiting the DNA polymerase [16, 17]. ② At low concentrations Ara-C continues synthesizing with DNA at a low speed, and binds with DNA chains competitively as a result of the cytotoxicity produced by Ara-CTP according to some studies. ③ Ara-U, a metabolite of Ara-C, can extend the phase S in the cell cycle and reduce the discharge of major drug ingredients from the kidneys, so as to prolong the drug effects. At the present stage, IDA combined with Ara-C has become the first choice for treatment of AML, but the IDA dose is always disputed [18]. In this study, three groups of AML patients were treated with different doses of IDA combined with Ara-C respectively, and the results showed that the ORR was 27.27% in the low-dose group, 54.55% in the medium dose group, and 60.61% in the high-dose group, among which the high-dose and medium-dose groups were significantly higher than the low-dose group, indicating significant differences between the groups, consistent with the results of relevant reports [19, 20]. Analysis of relevant factors affecting the early efficacy in AML patients proved that IDA at 10
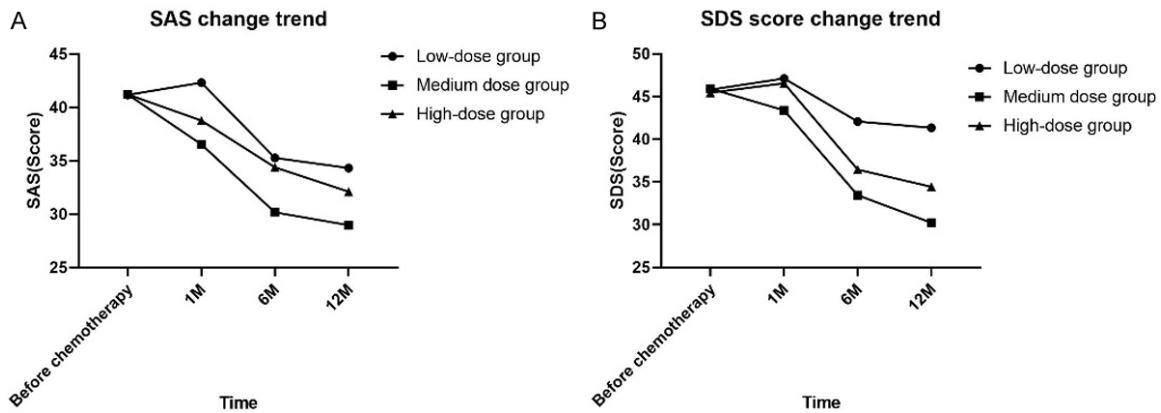
Figure 3. Changes in SAS and SDS scores before and after chemotherapy. There was no significant difference in SAS (A) and SDS (B) scores among the three groups before chemotherapy (P>0.05). At 1 month, 6 months and 12 months after treatment, SAS and SDS scores in the patients of the medium dose group were significantly lower than high-dose and low-dose groups (P<0.05). At the same time, the SAS and SDS scores of patients in the medium dose group showed a significant downward trend over time, with significant differences between the groups (P<0.05).

mg/m^2 was an independent factor of CR [21]. In addition to severe extramedullary toxicity, anthracyclines are also related to over-oxidization of panniculus adiposus due to anthracene nucleus being reduced to semiquinone free radicals, which accelerates the release of Ca^{2+}. Consequently, calcium overload takes place, inhibiting mitochondrial respiratory function and leading to hypoxic injury of cardiac muscle cells. Therefore, low-dose IDA is theoretically related with high safety [22, 23]. According to the results of this study, though the incidences of severe bone marrow suppression and infection in the low-dose group were lower than those in the medium dose group, there was no significant difference between the groups, indicating that the properly increased dose of IDA could improve the early efficacy and meet clinical requirements on safety at the same time. Subject to early adverse reactions, all patients had a poor quality of life with obvious anxiety and depression at the early stages after chemotherapy. Comparing the scores of QOL, SAS and SDS at 6 months and 1 year after treatment, it was found that the improvement of negative emotions was more apparent in the medium dose group, indicating that the appropriate dose of IDA combined with Ara-C could improve the long-term QOL of AML patients and alleviate their negative emotions.

As revealed by Kobayashi et al [24] in their study, under the influence of IDA induced bone marrow suppression, the incidence of various adverse reactions in the high-dose group was significantly higher than that in the medium-dose and low-dose groups, with a significant difference. This is also one of the main causes of high incidence of adverse emotions and low QOL in the high-dose group. The follow-up comparison of the three groups in this study showed that the low-dose group had the lowest 3-year survival rate of 30.30%; the middle dose group had the highest 3-year survival rate of 63.64%, and the high-dose group of 60.61% was slightly lower than the middle-dose group, which indicated that the high-dose and the medium dose groups were significantly higher than the low-dose group (P<0.05), but the difference between the high-dose and the medium dose groups was not significant (P>0.05). According to the analysis, this can be attributed to the fact that the low dose cannot achieve effective therapeutic effects, while high dose will directly increase the incidence of adverse reactions and affect the continuation of subsequent treatment.

In conclusion, the advantages of IDA at 10 mg/m^2 combined with Ara-C in treating AML include improvement of early CRR, acceleration of recovery of QOL and unhealthy emotions, satisfactory safety and high long-term survival rate.

Disclosure of conflict of interest

None.

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