CURATIVE EFFECT AND SAFETY OF 2-CDA, ARA-C AND G-CSF COMBINED TREATMENT FOR RELAPSED REFRACTORY ACUTE MYELOID LEUKEMIA

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ABSTRACT

Objective*: To investigate the curative effect and safety of purine analogues-Cladribine (2-CdA), cytosine arabinoside (Ara-C) and granulocyte colony-stimulating factor (G-CSF) combined treatment of relapsed refractory acute myeloid leukemia (AML).*

Methods: *Eighty-four patients with relapsed refractory acute myeloid leukemia treated in the Department of Hematology of our hospital from July 2017 to July 2018 were selected for this study, and randomly divided into the control group (n=42) and the study group (n=42). The control group was treated with FLAG (Fludarabine + Ara-C + G-CSF) protocol and the study group was treated with CLAG (2-CdA + Ara-C + G-CSF) protocol to analyze and compare the curative effect and safety of the two groups of patients with relapsed refractory acute myeloid leukemia.*

Results: *After two courses of treatment, in the study group, complete remission (CR) was 38.10%, partial remission (PR) was 54.76% and no remission (NR) was 7.14%; and in the control group, CR was 19.05%, PR was 47.62% and NR was 33.33%. The overall response (OR; CR + PR) of the study group was 92.86%, which was significantly higher than that of the control group (66.67%), and the difference was statistically significant (P<0.01). During the course of treatment, the incidence of adverse reactions such as infection, neutropenia, drug-induced liver injury, thrombocytopenia, nausea and vomiting, and mucocutaneous hemorrhage in the study group was significantly lower than that in the control group, with statistically significant differences (P<0.01). After one year of follow-up, it was found that the total survival time and recurrence-free survival time in the study group were remarkably higher than those in the control group, the mortality rate was lower than that in the control group, and the survival rate was higher than that in the control group, and the difference was statistically significant (P<0.05).*

Conclusion: *The treatment of relapsed refractory AML with 2-CdA, Ara-C and G-CSF regimen has better curative effect, higher safety and better prognosis, and can therefore be widely used in clinical practice.*

Keywords: *2-CdA + Ara-C + G-CSF, treatment, relapsed refractory acute myeloid leukemia (AML), curative effect, safety.*

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Introduction

Acute leukemia is a malignant clonal disease caused by abnormal hematopoietic stem cells. A large number of abnormal primitive cells and leukemic cells appear in the bone marrow of patients with acute leukemia, normal hematopoietic function is inhibited, and symptoms such as anemia, bleeding, infection and infiltration appear[(1)]. Acute leukemia is classified into acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) according to the involved cell types. AML is more common in adults; ALL is more common in children[(2)]. Acute leukemia in China is dominated by AML, with an incidence of about 1.62/100,000[(3)]. The condition of acute leukemia progresses rapidly: without treatment, a patient's survival time is only approximately three months, and in severe cases, death may occur within days of diagnosis[(4)]. Although there are many treatment regimens and drugs for relapsed refractory AML, the efficacy and prognosis remain pessimistic, which has been an intractable issue in the clinical hematology department. Recently, the CLAG (2-CdA + Ara-C + G-CSF) protocol has attracted significant attention in medical circles both at home and abroad because of its efficacy and safety in the treatment

of relapsed refractory AML. The National Comprehensive Cancer Network Guidelines of the United States put forward CLAG as a first-line treatment for relapsed and refractory AML[5]. A trial was conducted in our hospital to study the efficacy and safety of the CLAG regimen in the treatment of relapsed refractory AML.

Data and methods

General information

Eighty-four patients with relapsed refractory acute myeloid leukemia treated in the Department of Hematology of our hospital from July 2017 to July 2018 were selected for this study.

Inclusion criteria:

• All patients met the diagnostic criteria in the Chinese Guidelines for the Diagnosis and Treatment of Relapsed Refractory Acute Myeloid Leukemia issued in 2017 by the Leukemia lymphoma group, Hematology branch of the Chinese Medical Association[6];

• Patients who have not achieved partial remission after two courses of treatment with standard induced remission regimens;

• Patients who relapsed within six months of initial remission, or six months after initial remission and who failed to be treated again with the original induction regimen;

• Patients with multiple relapses;

• Leukemia cells in bone marrow were more than 5%;

• Patients with a physical condition score of 0 to 2 points;

• The patients and their families were informed and signed the informed consent;

• Patients aged between 18 years old and 60 years old.

Exclusion criteria:

• Patients with acute promyelocytic leukemia;

• Patients with severe liver and kidney dysfunction;

• Patients complicated with malignant tumor;

• Patients who were severely infected;

• Patients complicated with metabolic diseases;

• Patients who refused to participate in this study.

The patients were randomly divided into the control group and the study group. There were 42 cases in the control group, including 22 males and 20 females, with the mean age of (42.26±15.41) years old, and the average BMI value was (20.13±1.25) Kg/m^2. There were 42 cases in the study group, including 21 males and 21 females, with the average age of (43.05±14.39) years old, and the average BMI value was (20.15±1.21) Kg/m^2. There was no significant difference in age, sex and BMI value between the two groups of patients with relapsed refractory AML (P>0.05). The data are shown in Table 1.

Groups	Age (years)	Sex (cases)		BMI value (Kg/m^2)	FAB classification (cases)			
		Male	Female		M1	M2	M3	M4
Control group (n=42)	42.26±15.41	22	20	20.13±1.25	3	6	7	4
Study group (n=42)	43.05±14.39	21	21	20.15±1.21	3	7	7	3
t/χ^2	0.246	0.048		0.074	0.22			
P	0.806	0.827		0.941	0.974			

Table 1: Comparison of general data of the two groups of subjects ($\bar{x}\pm s$).

Method

The control group was treated with FLAG (Fludarabine + Ara-C + G-CSF) regimen: From day one to day six of treatment, patients were given a subcutaneous injection of 300μg of granulocyte colony stimulating factor (G-CSF; Qilu Pharmaceutical Factory; Batch number: 20033040; Specification: 150μg: 0.6mL/dose) once a day. On the second to sixth days of treatment, patients were given an intravenous drip of 25mg/m^2 of Fludarabine (Shanxi Pude Pharmaceutical Co., Ltd.; Batch number: SFDA approval number H20067309; Specification: 50 mg/dose) and 1g/m^2 of cytosine arabinoside (Ara-C; ActavisItaly S.p.A.; Batch number: H20100594; Specification: 0.1g/1 bottle/1 box) once a day. Four weeks is a course of treatment; patients were treated for two courses.

The study group was treated with CLAG regimen: From day one to day six of treatment, patients were given a subcutaneous injection of 300μg of G-CSF (Qilu Pharmaceutical Factory; Batch number: 20033040; Specification: 150μg:0.6mL/dose) once a day. On the second to sixth days of treatment, patients were given an intravenous drip of 5mg/m^2 of Cladribine (2-CdA; Zhejiang Haizheng Pharmaceutical Co., Ltd.; Batch number: H20052240; Specification: 10 mL: 10 mg cladribine and 90 mg sodium chloride) and 2g/m^2 of Ara-C (ActavisItaly S.p.A.; Batch number: H20100594; Specification: 0.1g/1 bottle/1 box) once a day. Four weeks is a course of treatment; patients were treated for two courses.

Observation indicators

Efficacy

The clinical manifestations, liver and kidney

function, blood routine and bone marrow cytology before and after treatment were observed. The efficacy was evaluated based on the criteria for the diagnosis and efficacy of hematologic diseases[7], and were divided into complete remission (CR), partial remission (PR) and no remission (NR). CR + PR = overall response (OR). The efficacy of the two treatment regimens was compared.

Safety

The occurrence of adverse reactions such as infection, neutropenia, drug-induced liver injury, thrombocytopenia, nausea and vomiting, and mucocutaneous hemorrhage was observed and recorded. The safety of the two treatment schemes was compared.

Prognosis

The total survival time, recurrence-free survival time and death of the patients were observed by one-year follow-up, and the prognosis of the two groups was compared.

Statistical methods

All the data of this study were analyzed by SPSS20.0 software package. The measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), using the t test for comparison between groups.

The counting data were expressed in terms of percentage (%), using the χ^2 test for comparison between groups. The ranked data were compared using the Ridit test. P<0.05 indicated the difference was statistically significant.

Results

Comparison of curative effect after treatment between the two groups

After two courses of treatment, in the study group, CR was 38.10%, PR was 54.76% and NR was 7.14%; and in the control group, CR was 19.05%, PR was 47.62% and NR was 33.33%. The OR of the study group was 92.86%, which was significantly higher than that of the control group (66.67%), and the difference was statistically significant (P<0.01). The results are shown in Table 2.

Groups	n	CR	PR	NR	OR
Control group	42	8 (19.05%)	20 (47.62%)	14 (33.33%)	28 (66.67%)
Study group	42	16 (38.10%)	23 (54.76%)	3 (7.14%)	39 (92.86%)
χ^2	0.003				8.924
P					

Table 2: Comparison of curative effect after treatment between the two groups (cases, %).

Comparison of adverse reactions during treatment between the two groups

During the course of treatment, the incidence of adverse reactions such as infection, neutropenia, drug-induced liver injury, thrombocytopenia, nausea and vomiting, and mucocutaneous hemorrhage in the study group was significantly lower than that in the control group, with statistically significant differences (P<0.01). The results are shown in Table 3.

Groups	n	Infection	Neutropenia	Drug-induced liver injury	Thrombocytopenia	Nausea and vomiting	Mucocutaneous hemorrhage
Control group	42	11 (26.19%)	12 (28.57%)	7 (16.67%)	10 (23.81%)	13 (30.95%)	11 (26.19%)
Study group	42	3 (7.14%)	4 (9.52%)	1 (2.38%)	2 (4.76%)	5 (11.90%)	3 (7.14%)
χ^2		5.055	4.941	4.822	8.473	4.525	5.055
P		0.025	0.026	0.028	0.004	0.334	0.025

Table 3: Comparison of adverse reactions during treatment between the two groups (cases, %).

Comparison of prognosis between the two groups of patients

After one year of follow-up, it was found that the total survival time and recurrence-free survival time in the study group were remarkably higher than those in the control group, the mortality rate was lower than that in the control group, and the survival rate was higher than that in the control group, and the differences were statistically different (P<0.05). The results are shown in Table 4.

Groups	n	Total survival time (months)	Recurrence-free survival time (months)	Deaths (cases)	Survival (cases)
Control group	42	5.25±2.56	3.42±2.12	18 (42.86%)	24 (57.14%)
Study group	42	9.21±3.41	6.35±2.85	8 (19.05%)	34 (80.95%)
t/χ^2		6.018	5.345	5.57	
P		<0.001	<0.001	0.018	

Table 4: Comparison of prognosis between the two groups of patients.

Conclusion

The prognosis of patients with relapsed refractory AML is extremely poor: the three-year total survival rate is just 10%, which is closely related to chemotherapy tolerance such as energy-dependent efflux pump on the cell membrane, apoptosis tolerance and FMS-like tyrosine kinase 3 mutation. 2-CdA is a kind of chloropurine analogue, which can selectively kill cells with higher deoxycytidine kinase content than deoxynucleotide enzyme by damaging mitochondria. 2-CdA has a remarkable effect on cell damage of leukemia cells in quiescent stage

and division stage. It can exert a certain inhibitory effect on DNA methylation transferase, consume methyl donors to play the role of demethylation, and promote cell apoptosis to a certain extent, and it is highly specific for lymphocytes[8].

2-CdA can effectively treat AML, CLL, hairy cell leukemia and non-Hodgkin's lymphoma as well as other lymphocytic proliferative diseases, and it has a weak effect on solid tumors. The main adverse reactions are bone marrow suppression and renal toxicity[9]. Ara-C is a pyrimidine-like anti-metabolizing drug, which has an obvious inhibitory effect on leukemia cells, mainly acts on the S proliferation phase of cells, and has a certain inhibitory effect on the synthesis of cell DNA, thus interfering with cell proliferation[10]. After Ara-C enters the human body, it is transformed into ara-CTP and cytarabine diphosphate under the action of kinase phosphorylation. The former has a certain inhibitory effect on the synthesis of DNA polymerase, while the latter can inhibit the transformation of CDP into DCDP, thus inhibiting the DNA polymerization and synthesis of cells[11]. Ara-C is mainly used in acute myeloid leukemia, acute monocytic leukemia and acute lymphoblastic leukemia, and is generally used in combination with other drugs[12].

G-CSF is a kind of glycoprotein, mainly produced by endotoxin, TNF-α and IFN-γ activated monocytes and macrophages, which plays an important role in the proliferation, differentiation and activation of hematopoietic cells in neutrophil lines, and can also promote the proliferation and differentiation of hematopoietic progenitor cells[13]. G-CSF is clinically used as an effective drug for the treatment of leukopenia, bone marrow hematopoietic dysfunction, myelodysplastic syndrome and infection caused by leukopenia after radiotherapy and chemotherapy of AML and tumors[14].

In this study, CR was 38.10%, PR was 54.76% and NR was 7.14% in the study group, and CR was 19.05%, PR was 47.62% and NR was 33.33% in the control group. The OR of the study group was 92.86%, which was significantly higher than that of the control group (66.67%), and the difference was statistically significant (P<0.01). These results suggest that the CLAG treatment plan has a remarkable curative effect and can improve the cure rate of patients, which is similar to the research results of Chen Wenkun and Zhang Yanbin[15]. By comparing the adverse reactions during the course of treatment, it was found that the incidence of adverse reactions such as infection, neutropenia, drug-induced liver injury, thrombocytopenia, nausea and vomiting, and mucocutaneous hemorrhage in the study group was significantly lower than that in the control group, with statistically significant differences (P<0.01).

It is indicated that the CLAG treatment plan has less adverse reactions, high safety, and can reduce the pain of patients. After one year of follow-up, it was found that the total survival time and recurrence-free survival time in the study group were remarkably higher than those in the control group, the mortality rate was lower than that in the control group, and the survival rate was higher than that in the control group, and the differences were statistically significant (P<0.05). It is suggested that the CLAG treatment regimen has a good prognosis, and the patients' survival time is long, which can increase the lifespan of patients.

In conclusion, the CLAG treatment plan of relapsed refractory AML has good curative effect, less adverse reaction, high safety and good prognosis, can prolong the life of patients, and can be widely used in clinical practice. However, due to the small sample size and short duration of this study, it is necessary to increase the sample size and follow-up time in future studies to observe the long-term efficacy of the CLAG regimen in the treatment of relapsed refractory AML.

References

1) Deeren D, Balabanov S, Nickel K, Giannopoulou C, Gonzalez-McQuire S, et al. Management of patients with acute lymphoblastic leukemia in routine clinical practice: Minimal residual disease testing, treatment patterns and clinical outcomes in Belgium, Greece and Switzerland. Leuk Res 2020; 91: 106334.
2) Sajdyk TJ, Boyle FA, Foran KS, Tong Y, Pandya P, et al. Obesity as a Potential Risk Factor for Vincristine-induced Peripheral Neuropathy. J Pediatr Hematol Oncol 2019; 1: 18.
3) Fleischmann M, Schnetzke U, Schrenk KG, Schmidt V, Sayer HG, et al. Outcome of FLT3-ITD-positive acute myeloid leukemia: impact of allogeneic stem cell transplantation and tyrosine kinase inhibitor treatment. J Cancer Res Clin Oncol 2017; 143: 337-345.
4) Lou JW, Philp L, Hou W, Walsh CD, Liu J, et al. Highlights from the latest in nanomedicine research. Nanomedicine (Lond) 2018; 13: 977-980.

5) Duan MH, Zhang Y, Zhang M, Han X, Zhang Y, et al. Efficacy and safety analysis of the combination of cladribine, cytarabine, granulocyte colony-stimulating factor (CLAG) regime in patients with refractory or relapsed acute myeloid leukemia. Chin J Hematol 2016; 37: 571-575.
6) Leukemia & Lymphoma Group, Chinese Society of Hematology. The guidelines for diagnosis and treatment of acute myelogenous leukemia(relapse/refractory) in China (2017). Chin J Hematol 2017; 38: 183-184.
7) Peng J, Yuan RL, Wang XQ, Wu F, Guo X. Detection of expression levels of microRNA-181a and microRNA-20a in serum of patients with multiple myeloma and its clinical significance. J Jilin Univ 2015; 41: 625-630.
8) Seiter K, Ahmed N, Shaikh A, Baskind P, Liu D. CLAG-based induction therapy in previously untreated high risk acute myeloid leukemia patients. Leuk Res 2016; 46: 74-78.
9) Bao Y, Zhao J, Li ZZ. Comparison of clinical remission and survival between CLAG and FLAG induction chemotherapy in patients with refractory or relapsed acute myeloid leukemia: a prospective cohort study. Clin Transl Oncol 2018; 20: 870-880.
10) Donovan SK. Four billion years and counting: canada's geological heritage, edited by Robert Fensome, Graham Williams, Aïcha Achab, John Clague, David Corrigan, Jim Monger and Godfrey Nowlan. Canadian Federation of Earth Sciences and Nimbus Publishing, Halifax, Nova S. Geological J 2016; 51: 160-161.
11) Gao F, Du MZ, Li G, Xie J, Ren JJ, et al. Clinical observation of CLAG regimen in treatment of relapsed or refractory acute myeloid leukemia. J Mod Oncol 2018; 7: 1075-1078.
12) Liu ZY, Chen Y, Chen YB, Yan ZY, Wang Y, et al. Efficacy and safety of the treatment regimen combining cladribine, cytarabine and granulocyte colony stimulating factor in patients with refractory or relapsed acute myeloid leukemia. J Int Med Concepts Pract 2019; 14:116-120.
13. Luo WF, Yu HL, Zou XL, Ni X, Wei J. Comparative observation of CLAG and FLAG regimen for relapsed refractory acute myeloid leukemia. Shandong Med J 2018; 58: 79-82.
14) Volkmann J, Schmitz J, Nordlohne J, Dong L, Helmke A, et al. Kidney injury enhances renal G-CSF expression and modulates granulopoiesis and human neutrophil CD177 in vivo. Clin Exp Immunol 2020; 199: 97-108.
15) Chen WK, Zhang YB, Duan MH. Nursing care of patients with refractory or relapsed acute myeloid leukemia undergoing treatment of CLAG regimen. J Nurs Sci 2017; 32: 38-40.

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