A Study of the Complete Response Rate with a Combination of High Dose Cytarabine and Cladribine in Refractory and Relapsed Acute Leukemia

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Abstract

Introduction: Acute leukemia covers a broad spectrum of hematological clonal diseases originating from the malignant transformation of stem cells. Current chemotherapeutic methods result in an incomplete response to primary regimens in 30-40% of cases.

Methods: 20 patients who had been diagnosed with acute leukemia and who had displayed defined criteria in order to enter our study, were assessed in a clinical trial. A combined chemotherapy regimen with Cladribine and Cytarabine was used in the evaluation of the response to treatment and other parameters between the two ALL (acute lymphoblastic leukemia) and AML (acute myeloid leukemia) groups.

Results: Average patient age was 32.5±11.3. 13 patients (65%) were male and 7 patients (35%) were female. The average blast count was 67.7% ±18.3% in the AML group while this count was 63.8±19.6% in the ALL group. 5 out of 11 (45.5%) AML patients and 4 out of 9 ALL patients (44.4%) died during our experiment with no significant statistical difference between the two groups (P=0.65). 4 of the AML patients (36.4%) showed complete response while 4 cases (36.4%) were refractory. In the ALL group, there were 3 patients (33.3%) with complete response and 5 (55.6%) were refractory cases.

Conclusion: According to the results of the present study compared to other similar studies, a combined chemotherapy regimen of Cladribine and Cytarabine can be used in acute relapsed and refractory leukemia, however, with high toxicity and high early mortality. If factors are controlled, mortality can be reduced in some cases.

Keywords: Acute Leukemia, Chemotherapy Regimen, Mortality

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Introduction

Acute leukemia is one of the most common malignancies affecting children and adults but with high mortality rates, especially in cases of a poor primary response to chemotherapy (CT) regimens. In the treatment acute myeloid leukemia, the first line CT regimen consists of D1-D3 Daunorubicin 60-45 $^{mg}/_{m2}$ and D1-D7 Cytarabine 200-100 $^{mg}/_{m2}$ with a 47% remission rate, reaching only 69% after second injections.(1) In other words, many cases are refractory from the onset and many of them show relapse in follow up programs requiring salvage CT regimens.(2) The aforementioned protocol shows more beneficial characteristics, among which are availability, efficacy and the synergistic effects of Cladribine on Cytarabine through the increase of ara-CTP in blast cells.(3)

In acute lymphoblastic leukemia, although primary complete response rates are different due to different treatment options, Fludarabine, Cytarabine and Cladribine are the drugs of choice in most salvage regimens.(4)

Looking more closely at acute leukemia prevalence, the 30- 40% unresponsiveness in primary CT sessions, the disease relapse rate and the need for salvage regimens of acceptable toxicity, weare urged to apply the mentioned regimen in acute leukemia.

Cytarabine and Cladribine (being readily available in different areas of our country) have known efficacy and combined synergistic effects. The side effects were also evaluated in the present research. The paucity of information on the efficacy of this regimen in our local area caused an assessment of the complete response rate to the regimen in acute refractory and relapsed leukemia.

Material and Methods

20 known cases of acute leukemia had been referred to Tehran's Valie-asr Hospital, where the patients were evaluated during a clinical trial. The study was completed in the Hematology- Oncology and Bone Marrow Transplantation Center of the Tehran University of Medical Sciences.

A central venous line was used for all patients. Cladribine was infused 5 $^{mg}/_{m2}$ in 2 hours during a period of 5 days if there were no contraindications. During the infusion of Cladribine over a 4 hour period, Cytarabine was infused during the same session (2 $^{g}/_{m2}$ in 2 hours) and G-CSF was included in the regimen from the 6^{th} day in 5 $^{U}/_{Kg}$ subcutaneous doses until it reached a count of over 1500 PMN.

Evaluating bone marrow samples, which had been aspirated on the 14^{th} day of the regimen, blast counts below 5% were considered CR, while counts over 25% were refractory and counts of between 5-25% were considered partial response results and patients were put on the same course once more. Counts of over 5% that had been measured again made the patient a refractory case. If the 14^{th} day samples were inconclusive, BMA was repeated 7 days later.

Acquired data is defined as Mean ± SD, frequency and percentage. SPSS.16. was the software used to analyze the data. Student t-test and Qi-square test (the Exact Fischer test as needed) were applied for quantitative and qualitative variables, respectively. Results were considered significant if $P<0.05$.

Results

20 patients were evaluated during and after prescription of the combined CT regimens. The results are as follows:

Age and gender description: 13 (65%) were male and 7 (35%) were female. The average age was 32.5±11.3 in the range of 20-68. 11 (55%) were AML cases and 9 (45%) were ALL cases. In the AML group, 3 patients were M_2, 6 were M_4 and 2 were M_5 subtypes.

Disease type and Cytogenetic: In the AML group, 7 patients (63.7%) were primary refractory and 4 patients (36.4%) were relapse one. 2 patients (22.3%) of ALL group were primary refractory, 3 (33.3%) were relapse one and 4 (44.4%) were relapse two. Cytogenetically, 7 cases (70%) of the AML group were classified as intermediate, 1 (10%) was classified as good and 2 (20%) were classified as poor. From the 9 ALL patients, 6 (75%) were classified as intermediate and 2 (25%) as poor. One patient out of each group wasn't assessed cytogenetically.

Para clinical parameters before CT: The average blast count was 67.7%±18.3% (25-100) in the AML group and 63.8±19.6% in the ALL group. Average hemoglobin count measured in the AML patients were 9.7±1.4 (7.3-11.7) and 10.7±1.5 (9–13) in the ALL patients. Average platelet count before CT were 107,000 (15,000- 60,000) in the AML group and 96,000 (16,000-200,000) in the ALL group.

The WBC count in 4 of the AML patients (36.4%) was below 4,000 and 4000 to 10,000 in 2 of the cases (18.2%) and over 10,000 in 6 (66.7%). Other parameters are compared and described in Table- 1.

Treatment Complications: Complications are shown in Table- 2 regarding both groups. Five (45.5%) of the AML and 4 (44.4%) of the ALL patients died. This statistics were not significantly different between the two groups ($P=0.65$). Five of the expired patients were of the refractory type and 4 were relapsing type without a significant difference ($P=0.54$).

In the present study, 5 patients with AML (4 cases in the primary refractory category and 1 case in the relapse category) and 4 patients with ALL (1 case in the primary refractory category and 3 cases In the relapse category) died. Causes of mortality are described in Table- 3.

Discussion and Conclusion

General Conclusion: Four (36.4%) of the AML patients showed a complete response while 4 (36.4%) were refractory. As mentioned before, response to CT was inconclusive in 3 of the cases. 3 (33.3%) of the ALL cases had a complete response and 5 (55.6%) were refractory. There was one inconclusive case in this group (Table- 4).

Table- 1: Para clinical parameters in AML and ALL patients

Parameter	AML, No.=11	ALL, No.=9	P- value
Cr	0.8 ± 0.2	0.8 ± 0.2	P=0.89
Alb	4 ± 0.2	3.8 ± 0.2	P=0.15
AST	37.6 ± 15.8	40.6 ± 13.4	P=0.65
ALT	23.2 ± 6.9	39.2 ± 22.5	P=0.03
Total Bil	0.7 ± 0.1	0.7 ± 0.4	P=0.67
Direct Bil	0.2 ± 0.05	0.2 ± 0.08	P=0.18

Cr= Creatinine, Alb= Albumin, AST= Aspartate transaminase, ALT= Alanine transferase, Bil= Bilirubin

Table 2: Regimen complications in AML and ALL patients

Type of Complication	AML (No.= 11)	ALL (No.= 9)	P- value
Nausea and Vomiting	9 (81.8%)	7 (77.8%)	P= 0.62
Diarrhea	--------	--------	--------
Mucositis	7 (63.6%)	5 (55.6%)	P= 0.53
Hepathotoxicity	2 (18.2%)	--------	P= 0.003
Alopecia	8 (72.7%)	6 (66.7%)	P= 0.57
Nephrotoxicity	--------	--------	--------
Bleeding	3 (27.3%)	2 (22.2%)	P= 0.61
Infection	8 (72.7%)	6 (66.7%)	P= 0.58
Neurotoxicity	--------	2 (22.2%)	P= 0.013

AML: Acute myelogenous leukemia, ALL: Acute lymphocytic leukemia

Table- 3: Causes of death in AML and ALL patients

Cause of death	Aspeigiloma	Mucoromycosis	ICH	Sepsis	Pneumonia
Number	1 patient	1 patient	1 patient	4 patient	2 patient
Type of disease	Primary Refractory AML	Primary Refractory AML	Primary Refractory AML	Relapsed and Refractory AML, ALL	Relapsed AML, ALL
Time of death (day)	32	29	18	50, 28, 18, 14	23, 12

AML: Acute myelogenous leukemia, ALL: Acute lymphocytic leukemia

Table- 4. Treatment response after chemotherapy based on bone marrow aspiration.

Day of BMA	CR	Refractory	Hypocellular	No. BMA
14	----------	9	7	4
21	4	9	3	4
28	6	9	1	4
35	6	9	1	4
42	7	9	----------	4

BMA: Bone marrow aspiration, CR: Compelete remission

Table- 5. Final clinical parameters in AML and ALL patients

Variable	AML	ALL	P value
Pack cell after CT(Unit)	15.2 ± 10.2	10.6 ± 8	P=0.60
Platelet after CT(Unit)	84.7 ± 29.1	100.3 ± 85.7	P=0.009
Platelet under 20000(day)	16.7 ± 8.4	15.7 ± 9.9	P=0.48
PMN under 500(day)	10.7 ± 4.3	12.1 ± 4.4	P=0.66
Admission time(day)	28.1 ± 11.7	27.6 ± 11.3	P=0.81

AML: Acute myelogenous leukemia, ALL: Acute lymphoblastic leukemia, CT: Chemotherapy

Table- 6.Comparing salvage chemotherapy regimens in acute leukemias and their mortality rates

Author	Regimen	CR	Refractory	Mortality
Specchia et al.	FLAG-IDA	39.1%	56.5%	1 patient
Wrzesien et al.	Cytarabine+Cladribine	50%	33%	8 patients
Safaei et al.	Cytarabine+Cladribine	35%	45%	9 patients

FLAG-IDA: Fludarabine, Cytarabine, Idarubicin

Final clinical results are discussed in Table- 5 regading the AML and ALL groups.

Current salvage regimens for adult patients induced complete remission (CR) only in 20-50% of the

cases while the remission phase was prolonged less than 4 months. The best treatment in such cases was the one with the least toxicity inducing CR.(5)

In the present study, a combined CT regimen of Cytarabine and Cladribine was evaluated in refractory acute leukemia patients.

Four AML patients (36.4%) had a complete response and 4 (36.4%) were refractory while 3 (33.3%) of the ALL cases had complete response and 5 (55.6%) were refractory.

Specchia, et al, had studied a CT regimen called FLAG-IDA in a detailed regimen consisting of Fludarabine, Cytarabine, G-CSF and Idarubicin.(5) 39.1% of the cases were in CR while 56.6% were refractory after undergoing the salvage regimen. One patient died due to infection in the aplastic phase. The average neutropenic phase (under 500) was 10.7 days in the AML group and 12.1 days in the ALL group in our study (Table- 6).

The average thrombocytopenic phase (under 20,000) was 23 days ranging from 19 to 25 days in the study of Specchia, et al. This was 16.7 days in the AML group and 15.7 days in the ALL group in our study.

Estimation of the CR rate of the two groups considered the complication rates. The combined regimen used in the present approach seemed to induce CR as the FLAG-IDA regimen had, with high toxicity.

In another study, Wrzesien, et al, a combined CT regimen similar to ours regarding refractory AML cases was evaluated.(6) Average patient age was 45, ranging from 18 to 67 years. In our study, the average age was 32.5±11.3 (20 to 68 yrs). Fifty patients were of the primary refractory type and 8 were relapsing type (6 patients were relapse 1 and 1 patient was relapse 2). The complete remission rate was 50% (29 patients) in Wrzesian's study and 33% were refractory after CT.

According to the results of the present study compared to other similar studies, a combined chemotherapy regimen of Cladribine and Cytarabine can be used in acute relapsed and refractory leukemia but with high toxicity and high early mortality rates. If factors are controlled, mortality can even be reduced in some cases.

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