Original Article

The mortality and response rate after FLANG regimen in patients with refractory/relapsed acute leukemia

Vali A. Mehrzad, Lida Liaghat, Farzaneh Ashrafi, Mehdi Tazhibi[1], Mehri Hajalikhani, Neda Alijanian

Department of internal medicine, Alzahra Hospital, [1]Health department, Isfahan Universityy of medical sciences, Isfahan, Iran

Abstract

Background: Oncologists today are greatly concerned about the treatment of relapsed/refractory acute leukemia. FLANG regimen, combination of novantron, cytarabine, fludarabine, and granulocyte-colony stimulating factor, has been used in treatment of refractory/relapsed acute leukemia since 1990s. The present study has evaluated mortality and response rate of this regimen.

Materials and Methods: In this study, 25 patients with refractory/relapsed acute leukemia aged 15-55 years underwent FLANG regimen at Seyed-Al-Shohada Hospital, Isfahan, Iran during 2008-2009. One month later, bone marrow samples were taken to evaluate the responsiveness to treatment. Participants were followed for a year. The data was analyzed by student-t and chi-square tests, logistic, and Cox regression analysis, and Kaplan-Meier curves in SPSS $_{19.}$

Results: Out of the 25 patients, 8 patients (32%) had acute lymphoblastic leukemia (5 refractory and 3 relapsed cases) and 17 subjects had acute myeloid leukemia (7 refractory and 10 relapsed cases). According to the bone marrow biopsies taken one month after FLANG regimen, 10 patients (40%) had responded to treatment. Five patients of the 10 responders underwent successful bone marrow transplantation (BMT). On the other hand, 13 patients (52%), who had not entered the CR period, died during the follow-up. Logistic regression analysis did not reveal any significant associations between disease type and responsiveness to treatment.

Conclusion: This study indicated higher rates of unresponsiveness to treatment while its mortality rate was comparable with other studies. Overall, according to limitations for BMT (as the only chance for cure) in Iran, it seems that FLANG therapy is an acceptable choice for these patients.

Key Words: Bone marrow transplantation, FLANG regimen, Refractory acute leukemia, Relapsed acute leukemia

Address for correspondence:
Dr. Lida Liaghat, Department of internal medicine, Alzahra Hospital, Isfahan Universityy of medical sciences, Isfahan, Iran E-mail: lida.liaghat@gmail.com
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INTRODUCTION

Leukemia is among the most important oncological disorders in today's world. An appropriate method for treating patients with refractory/relapsed leukemia is of great concern.[1] Unfortunately, 10-25% of acute leukemia patients are resistant to treatment (refractory cases).[2] In addition, despite advances in treatment of acute leukemia, not more than 30-40% of patients would

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live a long life.[3] Disease relapse occurs in 20-70% of acute myeloid leukemia (AML) cases[4,5] Almost half of acute lymphoblastic leukemia (ALL) sufferers die. In addition, after entering the complete remission (CR) period, one third of patients still face a normal risk of relapse while two thirds are considered as high risk.[6,7] In such cases, treatment would be too difficult and the success rate of normal methods would be quite low. However, a combination of cytarabine (ara-C), fludarabine (F-AMP), and granulocyte colony-stimulating factor (G-CSF) and novantron called FLANG, has been used in the treatment of refractory/relapsed acute leukemia since 1990s.[8] These medications have synergic effects.[9] FLANG regimen is currently used for poor risk AML, myelodysplastic syndrome, and refractory/relapsed ALL patients.[10, 11] Since various studies have reported the complete remission rate to be 42-67% after FLANG, the method has been increasingly utilized in recent years.[8]

Leukemia has been observed in 8.5 and 6.1 out of every 1, 00,000 Iranian men and women, respectively.[12] However, few studies have evaluated refractory or relapsed leukemia in Iran. Therefore, the present study assessed the response and mortality rate after FLANG regimen.

MATERIALS AND METHODS

This study evaluated 25 patients with acute refractory or relapsed leukemia who were hospitalized in Seyed-Al-Shohada Hospital, Isfahan, Iran, during 2008-2009. Patients aged 15-55 years who underwent FLANG regimen.

Individuals aged 15-55 years were included if they did not respond to cytosine and anthracycline, and relapsed during the maintenance treatment period for ALL or within 6 months after induction therapy for AML. Patients older than 55 years of age, or with severe organ damage, including twice the normal alanine aminotransferase (ALT) or creatinine levels, left ventricular ejection fraction <50%, or low performance status were excluded. In addition, patients who were unwilling to participate were not enrolled.

Prior to the study, the participants were explained about treatment method, objectives of the research, and probable benefits and complications of the treatment. All the subjects underwent a FLANG regimen. They thus received intravenous (IV) F-AMP 30 mg/m^2 over 30 minutes on days 1-5, ara-C 2 g/m^2/day IV over 4 hours on days 1-5, novantron 10 mg/m^2/day IV on days 1-3, and G-CSF 5 μg/kg from day 0 until neutrophil count of ≥500 /mL.

During hospitalization, daily tests for complete blood count (CBC), blood urea nitrogen (BUN), creatinine (Cr), sodium (Na), and potassium (K) were performed to assess hematologic and non-hematologic side effects of FLANG regimen. Liver function test was also conducted before and one week after the study. Daily clinical examinations were performed and necessary paraclinical measures were taken. In case of fever, required tests were carried out and the patients were treated with antibiotics and antifungal medications if needed. Packed cell and platelet transfusion were prescribed for patients with platelet counts < 20000 or hemoglobin levels less than 7.

Bone marrow aspiration and biopsies were performed on the 28th day after FLANG regimen initiation to evaluate response to treatment. Bone marrow cellularity > 20%, bone marrow blast < 5%, absence of peripheral blood blasts (PBBs), and absence of extramedullary leukemic involvements were suggestive of CR. All patients were followed for a 1-year period during which the mortality rate was recorded.

The collected data was analyzed by student-t and chi-square tests to compare the two groups of relapsed and refractory. Cox analysis and Kaplan-Meier curves were also used to assess the survival rate. All analyses were performed in SPSS.[13]

Findings

This study evaluated a total number of 25 acute leukemia patients aged 29.48 ± 9.00. Males and females respectively constituted 48% (n = 12) and 52% (n = 13) of the studied population. Overall, 8 patients (32%) had ALL (5 refractory and 3 relapsed cases) and 17 subjects had AML (7 refractory and 10 relapsed cases).

Patients were hospitalized for a mean duration of 22.96 ± 7.69 days during which due to fever 14 individuals (56 %) received imipenem, 17 patients (68 %) received vancomycine and 10 (40%) received amphotricine. Patients received 16.52 ± 11.24 units of platelets and 9.36 ± 6.24 units of packed cells.

According to bone marrow aspirations and biopsies taken one month after FLANG regimen, 10 patients (40%) had responded to treatment, of which 5 individuals underwent successful bone marrow transplantation (BMT), 4 patients are in waiting list for BMT, and 1 individual unfortunately died due to the relapse of his disease while he was in the waiting list for BMT. On the other hand, 13 patients (52%), who had not entered the CR period, died during the follow-up [2 CNS hemorrhage, 2 ischial abscess, 3 sinusitis, 3 pneumonia and others with full blown

sepsis], and 2 (8%) patient are still alive without CR.

Table 1 compares the demographic characteristics, type of disease, treatment course, and death rate between patients who did or did not respond to treatment. Non-responsive patients experienced platelet counts less than 20000 and 50000 and polymorphonuclear leukocyte (PMN) counts less than 500 and 1000 for significantly more days. In addition, although death was not observed in responsive patients, 13 non-responsive cases (86.7%) died. In relapsed cases association of recurrence time (< 6 months and ≥ 6 months) and responsiveness to FLANG regimen was evaluated that showed no significant difference. Numbers of responsive AML and ALL individuals were not significantly different [8 (47.05%) vs. 2 (25%) cases].

Table 2 compares the studied variables between patients who died and those who survived. Similar to previous findings, an insignificant difference was observed in the number of deaths between the ALL and AML sufferers [6 (75%) vs. 7 (41.17%) deaths].

Mean duration of follow-up for all patients was 246.24 ± 132.57 days. Deaths occurred 143.23 ± 101.30 days after FLANG initiation and the longest period before death was 270 days. Only one patient died during the hospital stay (on day 13). However, 2 individuals died at the time of bone marrow biopsy after treatment, so only 3 patients (12%) died due to complications of FLANG chemotherapy.

Figure 1 illustrates Kaplan-Meier curves for death incidence among the 4 types of leukemia and Figure 2 illustrates the curve for all death during the follow-up period. As the figure shows, the quickest deaths were observed in the relapsed AML patients. The median time of death was 279 days.

Logistic regression analysis was used to determine the risk factors for unresponsiveness to treatment [Table 3]. The crude RR of each type of disease was measured and an adjusted regression model for age and sex was done to measure the adjusted RR for the type of disease.

The hazard ratio (HR) of disease type on death incidence was assessed by Cox regression analysis [Table 4]. In the first model, the crude values of HR were calculated. The second model for measuring the HR of disease was adjusted for age and sex, and in the third models the confounding effects of age, sex, platelet transfusion, antifungal therapy, and fever during hospitalization became adjusted.

Table 1: Comparison of demographic, treatment, and follow-up characteristics between patients with response and non response to FLANG regimen

	No response 15	Response 10	*P* value
Age*	30.20 ± 10.31	28.40 ± 6.96	0.617
Platelet > 20000 (days)*	3.93 ± 8.28	22.40 ± 8.07	<0.000
Platelet > 50000 (days)*	4.80 ± 10.24	25.30 ± 7.66	<0.000
PMN > 500 (days)*	4.67 ± 8.19	21.30 ± 5.41	<0.000
PMN > 1000 (days)*	5.33 ± 9.57	22.60 ± 5.85	<0.000
Platelet transfusion (unit)*	13.87 ± 11.02	20.50 ± 10.90	0.119
Packed cell transfusion (unit)*	9.47 ± 6.52	9.20 ± 6.12	0.889
Hospital stay (days)*	21.53 ± 8.24	25.10 ± 6.60	0.358
Disease**			0.650
ALL	6 (40.0)	2 (20.0)	
Refractory ALL	4 (26.7)	1 (10.0)	
Relapsed ALL	2 (13.3)	1 (10)	
AML	9 (60.0)	8 (80.0)	
Refractory AML	3 (20.0)	4 (40.0)	
Relapsed AML	6 (40.0)	4 (40.0)	
Relapse ≥ 6 months**	4 (26.7)	5 (50)	0.735
Fever **	13 (86.7)	9 (100)	0.511
Death**	13 (86.7)	0 (0)	<0.000
Gender (female) **	7 (46.7)	6 (60.0)	0.688

*Mean ± standard deviation **Number (%): in alive patients PMN: Polymorphonuclear cell ALL: Acute lymphoblastic leukemia AML: Acute myeloid leukemia

Table 2: Comparison of demographic, treatment, and follow-up characteristics between deadand alive patients

	Alive 12	Dead 13	*P* value
Age*	30.33 ± 7.79	28.69 ± 10.25	0.586
Platelet > 20000 (days) *	21.75 ± 7.60	1.69 ± 6.10	<0.000
Platelet > 50000 (days) *	24.58 ± 7.32	2.31 ± 8.32	<0.000
PMN > 500 (days) *	20.50 ± 5.45	2.85 ± 7.02	<0.000
PMN > 1000 (days) *	21.75 ± 5.84	3.46 ± 8.74	<0.000
Platelet transfusion(unit) *	17.92 ± 11.75	15.23 ± 11.06	0.548
Packed Cell transfusion (unit) *	9.00 ± 5.56	9.69 ± 7.01	0.891
Hospital stay (days) *	24.67 ± 6.15	21.38 ± 8.83	0.413
Disease**			0.523
ALL	2 (16.7)	6 (46.2)	
Refractory ALL	1 (8.3)	4 (30.8)	
Relapsed ALL	1 (8.3)	2 (15.4)	
AML	10 (83.3)	7 (53.8)	
Refractory AML	4 (33.3)	3 (23.1)	
Relapsed AML	6 (50.0)	4 (30.8)	
Gender (female) **	8 (66.7)	5 (38.5)	0.158
Fever **	11(100)	11 (84.6)	0.482
Response**	10 (83.3)	0(0)	<0.000

*Mean ± standard deviation **Number (%) PMN: Polymorphonuclear cell, ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia

DISCUSSION

The present study was designed to evaluate responsiveness to treatment and death rate in patients

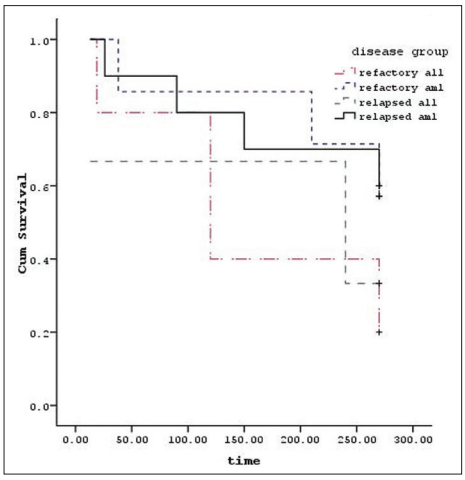

Figure 1: Kaplan-Meier curves of survival in 4 groups of leukemia in studied subjects

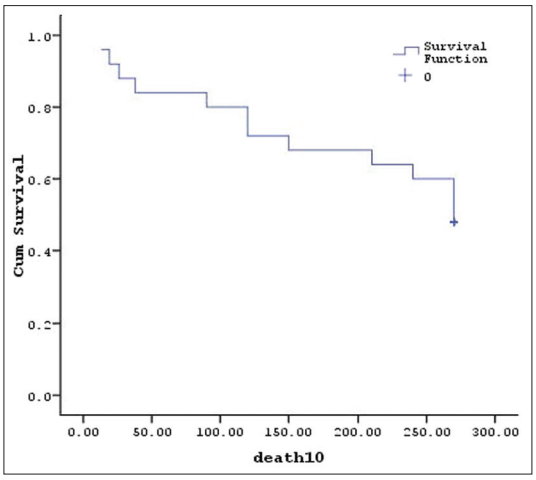

Figure 2: Kaplan-Meier curves of overall survival in studied subjects

Table 3: Relative risk of disease for response to FLANG regimen in patients with acute leukemia

	Refractory ALL	Refractory AML	Relapsed ALL	Relapsed AML
Crude Model	1	5.333 (0.375-75.776)	2.000 (0.076-51.593)	2.667 (0.212-33.486)
Adjusted based on age and sex	1	6.960 (0.365-132.697)	2.111 (0.078-57.197)	4.886 (0.223-107018)

ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia

Table 4: Hazard ratio of disease for death after FLANG therapy in patients with acute leukemia

	Refractory ALL	Refractory AML	Relapsed ALL	Relapsed AML
Crude model	1	0.383 (0.085-1.725)	0.852 (0.155-4.691)	0.373 (0.093-1.504)
Adjusted based on age	1	0.488 (0.087-2.728)	0.793 (0.142-4.415)	0.503 (0.099-1.059)
Adjusted based on all variables*	1	0.377 (0.40-3.562)	0.812 (0.129-5.089)	0.270 (0.023-3.098)

*Adjusted for age, sex, antifungal, platelet transfusion, and fever, ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia

with acute refractory/relapsed leukemia under FLANG regimen. It revealed that 40% of patients entered the CR period. However, 52% of patients died when they had not yet entered the CR period.

Prognosis of patients with acute leukemia is considered as poor. It has in fact been reported by previous studies as 29-44%.[14,15] FLANG regimen has been used since 1990 to increase the efficacy of leukemia treatments. It has been proved to be almost safe and efficient with a relatively high CR rate.[11,16] Most studies have indicated a CR rate of above 50% for FLANG. Suki *et al*. investigated the effects of F-AMP and ara-C therapy on refractory/relapsed ALL sufferers and found 30% of the patients to enter the CR period. They reported the median survival as 12 weeks.[17] Another study assessed the efficacy of FLANG on 23 relapsed or refractory AML patients aged 12-17.5 years. Following the treatment, 17 individuals entered the CR period. Then, 11 bone marrow transplantations were performed.[18] Likewise, Hashmi *et al*. treated 12 refractory or relapsed acute leukemia patients with FLAG-IDA regimen. They described 8 cases of CR (66.6%) from which 4 patients received BMT.[19] A similar research stated 52.1% of 46 refractory or relapsed patients under FLAG-IDA regimen to enter the CR period. BMT was received by 11 patients after remission.[13] On the other hand; few studies have found lower CR rates. For instance, Yalman *et al*. reported a CR rate of 17.6%.[20] Mortality rates have also varied from 41% to 87.5% in different studies.[19] Most previous studies, however, indicated higher CR rates than we did.[21-23]

Such inconsistencies might have been resulted by ethnical differences. In fact, since ara-C acts intracellularly, its effects can be influenced by genetic variations, i.e., the efficacy of ara-C depends on its intracellular concentration and access to DNA. The gene responsible for this process has been identified. [24] Therefore, genetical and ethnical dissimilarities are well expected to affect responsiveness to treatment.

Another point to bear in mind is the insufficiency of information toward the symptoms of leukemia and the time to refer for treatment. A study measured cancer-related knowledge among 2500 Tehran (Iran) residents selected by multistage random sampling. It

found a high level of knowledge only in 18.82% of the studied individuals.[25] This lack of knowledge results in late reference while the disease is much more advanced and unresponsive to treatment.

However, the similarity of mortality rates between our study and previous researches indicates appropriate follow-up, timely examinations and paraclinical tests, treatment of complications along with antibiotics and antifungal treatments in cases of bacterial or fungal infections during the CR period.

Unfortunately, we could not determine the risk factors for unresponsiveness to treatment and death. A larger sample size and the availability of a control group might be helpful in detecting the predictive factors.

CONCLUSION

BMT is the recommended treatment option for patients with relapse or resistant disease; it is clear that BMT will be more successful when done on patients who are in CR. In Iran we have only 5 centers (in Tehran including Shariati, Imam Khomeini and Taleghani Hospitals and so in Shiraz and Kerman), which are capable for performing BMT. Keeping in mind these facts besides considering the large number of patients all over Iran that need BMT, now in our country only the patients who are in CR can undergo BMT. In our study, the FLANG regimen has provided 40% chance for induction of CR in patients with refractory/relapsed leukemia and so, although the overall responsiveness to treatment in this study was lower than previous researches, considering that the mortality rates were similar, it seems that in Iran this regimen is a safe bridge for these patients toward BMT and cure. According to this fact that all patients with refractory/relapsed leukemia will die without BMT, we recommend FLANG chemotherapy for these patients.

In addition, we were unable to recognize the risk factors for unresponsiveness and death. Further clinical case-control trials with a larger sample size would probably lead to better results. Moreover, the society needs to be educated about the symptoms of leukemia. Sufferers are also required to be informed about the symptoms of relapse and untreated disease.

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