Immunopathologia Persa
http www.immunopathol.com
DOI:10.34172/ipp.2022.27272

Evaluation of FLANG versus mitoxantrone and etoposide for the treatment of refractory/relapsed acute leukemia

Valiollah Mehrzad[1,2], **Maryam Mirpourian**[1,2*], **Pegah Farrokhi**[3]

[1]Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Cancer Prevention Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[3]School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran

***Correspondence to**
Maryam Mirpourian,
Email:
dr.maryammirpourian@yahoo.com

Received 28 June 2021
Accepted 21 Dec. 2021
Published online 5 July 2022

Keywords: Acute leukemia, Salvage therapy, Mitoxantrone, Etoposide

Abstract

Introduction: Failure to respond to the chemotherapy and relapse occurrence is considerably high in acute leukemia as one of the most common hematologic malignancies requiring emergent efficacious well-tolerated salvage therapy. However, varieties of regimens have been investigated, since the best approach with an optimal response is a question.

Objectives: In our study, we aimed to compare the efficacy of FLANG (fludarabine, cytosine arabinoside, mitoxantrone and G-CSF) versus mitoxantrone and etoposide for the treatment of refractory/relapsed acute leukemia.

Patients and Methods: In this retrospective cohort study, 45 patients with acute leukemia were randomly divided into two groups of salvage therapy with FLANG (n=23) and mitoxantrone and etoposide (n=22). The patients were followed for five years. Progression-free survival, response to the treatment, chemotherapy-induced toxicity based on Criteria for Adverse Effects version 4 (CTCAE-4), and mortality were compared between the groups. Besides, to estimate the survival Kaplan-Meier curve and Cox regression were used.

Results: Comparison of the two regimens revealed insignificant differences in terms of response rate ($P=0.87$), chemotherapy-induced toxicity ($P=0.22$) and mortality rate ($P=0.26$) and etiology of mortality ($P=0.98$). The median progression-free survival following FALNG and the latter regimen was four months (95% CI: 3.183, 4.862) versus three months (95% CI: 1.777, 4.223; $P=0.38$), respectively.

Conclusion: Based on this study, the two salvage regimens of mitoxantrone plus etoposide and FLANG were similar in terms of complete remission, progression-free survival, and toxicity for the cases with refractory/relapsed acute leukemia.

Trial Registration: This study has been registered in the Iranian Registry of Clinical Trials and obtained code IRCT20190618043939N1 (https://en.irct.ir/trial/40272, Ethical code# IR.MUI.MED.REC.1398.586).

Citation: Mehrzad V , Mirpourian M, Farrokhi P. Evaluation of FLANG versus mitoxantrone and etoposide for the treatment of refractory/relapsed acute leukemia. Immunopathol Persa. 2022;x(x):e27272. DOI:10.34172/ipp.2022.27272.

Introduction

To date, leukemia is among the most common hematologic malignancy worldwide. Despite the signs of progress in the treatment of acute leukemia in recent years, appropriate treatment for refractory/relapsed leukemia is a significant concern for scientists (1). Unfortunately, approximately 25% of the leukemic patients are resistant to the standard chemotherapy regimens, and only 30-40% of them would experience a long-time life (2,3). It was estimated that 20-70% of the patients with acute myelogenous leukemia (AML) experience relapses. Besides, the estimated mortality rate for acute lymphoblastic leukemia (ALL) accounts for up to 50% (4). More notifying statistics represent that even in cases with complete remission, one-third have the average risk of relapse, and the more concerning rate of two-third are at high risk of relapse occurrence (5).

Most of the cases experiencing relapses undergo treatment with intensive high-dose multiagent chemotherapy. This trend, besides

Key point

Numerous cases with leukemia, regardless of its type, experience relapses or have refractory courses. These patients should be treated with high doses of multiagent regimens that lead to significant complications and impairs their quality of life. Accordingly, several investigations are in progress to figure out a regimen with the ultimate response and the least adverse effects. Accordingly, the current study aimed to compare the efficacy of FLANG (fludarabine, cytosine arabinoside, mitoxantrone and G-CSF) versus mitoxantrone plus etoposide regimens and found comparable outcomes in terms of achieving complete regimen, progression-free survival and toxicity.

its negative burden on the patient's quality of life, induces significant cumulative toxicity for the patients. Therefore, various studies have investigated different salvage regimens for the leukemic cases experiencing relapses (6).

Though there is not a unified theory about a particular regimen, studies in the literature have shown reasonable outcomes following the use of mitoxantrone and etoposide as monotherapy or in combination with other agents for the treatment of relapses occurred in acute leukemia (7).

Another regimen consisted of a combination of cytarabine (ara-C), fludarabine (F-AMP), and granulocyte colony-stimulating factor (G-CSF) and Novantrone is known as the FLANG (fludarabine, cytosine arabinoside, mitoxantrone and G-CSF) regimen. This regimen has been used for refractory/relapsed ALL and refractory/relapsed AML, but the considerable response rate of up to 67% complete remission has made physicians consider FLANG in more extensive ranges of their patients(5,8).

Objectives

Considering the significance of achieving complete remission and imposing the synergistic effect of the drugs to use the least effective dose and to minimize the chemotherapy-related toxicity, selection of the best therapeutic salvage remedy is crucial for this vulnerable population. To the best of our knowledge, the current report is the first one aimed to compare the efficacy and chemotherapy-related toxicity of mitoxantrone and etoposide versus FLANG for those with refractory/relapsed acute leukemia.

Patients and Methods

Study design

The current report is a randomized clinical trial conducted on 45 refractory/relapsed leukemia patients referred to Seyed-o-Shohada hospital, a tertiary oncology hospital in Isfahan, Iran, from January 2015 to March 2019. Therefore, the numbers of 15 patients with B-cell ALL, four ones with T-cell ALL, 25 ones with AML non-M3, and a person with undifferentiated leukemia met the inclusion criteria of this study.

Patients with 15-60 years old with a diagnosis of refractory (failure to achieve complete remission following initial induction chemotherapy) or relapsed acute leukemia, with the Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, serum creatinine <2 mg/dL, total serum bilirubin levels <2 mg/dL, and aspartate transaminase and alanine transaminase levels in the ranges <3 times of the upper limit of normal were included.

Secondary active malignancy other than leukemia, pregnancy or lactation was considered as the exclusion criteria.

Treatment before relapse

The induction chemotherapy included two standard protocols of 3+7 or hyper-CVAD [cyclophosphamide, vincristine, doxorubicin (Adriamycin), dexamethasone] explained in the followings; The standard protocol of induction chemotherapy for non-M3 AML, including a 7+3 regimen, cytarabine (AC) plus daunorubicin (DNR), was administered for all of the AML patients(9). Intravenous DNR was administered once daily for three consecutive days at a dose of 45–90 mg/m^2 for 30 minutes, and then AC was prescribed once daily at a dose of 100 mg/m^2 over 24 hours for seven consecutive days. Then, four courses of consolidation chemotherapy were administered for all of the non-M^3 AML patients with a protocol that included 3000 mg/m^2 intravenous AC over 1 hour every 12 hours for days 1, 3 and 5.

The ALL patients were treated with eight courses of hyper-CVAD regimen (course a consisted of days 1, 3, 5, and 7 and course b consisted of days 2, 4, 6, and 8), including intravenous cyclophosphamide 300 mg/m^2 every 12 hours for 6 doses, intravenous vincristine 2 mg on days 4 and 11; intravenous doxorubicin 50 mg/m^2 on day 4; and dexamethasone 40 mg daily on days 1 to 4 and 11 to 14 in 1st, 3rd, 5th and 7th courses, and high dose methotrexate plus cytarabine in the course b (11).

The patients were assigned into the groups treated with each of the salvage regimens using Random Allocation Software by which each patient was provided with a particular number allocated him/her to each of the groups.

Eventually, in cases with relapsed/refractory ALL or AML the following salvage therapy was administered.

FLANG therapy

FLANG regimen included five days of treatment with 30 minutes of fludarabine with a dose of 30 mg/m^2/day followed by an infusion of Ara-C with a dose of 2 g/m^2/day for 4 hours. Mitoxantrone was infused with the dose of 10 mg/m^2/day through 30 minutes on days 1-3 of the chemotherapy. G-CSF 5 µg/kg/day was subcutaneously administered once daily 12 hours before fludarabine administration for five days and then, once daily, until achieving the absolute neutrophil count of 1000 per liter or above.

Mitoxantrone plus etoposide

The second approach consisted of 10 mg/m^2 of daily infusion of mitoxantrone on 1-5 days with concurrent intravenous administration of 100 mg/m^2 of etoposide (7).

Further assessments

Prophylactic antibiotics (ciprofloxacin), antifungal (fluconazole), an antiviral (acyclovir) therapies were prescribed at the time of chemotherapy initiation. Besides, G-CSF 5 µg/kg/day was administered daily until the achievement of ANC (absolute neutrophil count) >1000 per liter.

Within 28 days after the chemotherapy, bone marrow aspiration/biopsy (BMA/B) and peripheral blood smear

(PBS) was obtained from the patients. All of the BMA/Bs and PBSs were interpreted by a skilled target hematologist to minimize the probability of inter-observer bias.

The response rate was divided into four subgroups of complete remission, partial remission (PR), no response, and early death.

Complete remission was defined as the presence of less than 5% blasts in the bone marrow, no blast in the peripheral blood smear, and no extranodulary involvement. Five to 25% blasts of BMA/B were considered as partial remission, and the presence of over 25% of blasts in the bone marrow was defined as no response.

Early death was defined as the incidence of death within the first 6 weeks of chemotherapy initiation.

The incidence of death within less than six weeks following the initiation of the second salvage therapy was considered as early death. The definition of progression-free survival was the duration between the initiations of complete remission until the recurrence of relapse or death.

The chemotherapy-related hematologic toxicity was assessed based on the Common Terminology Criteria for Adverse Effects version 4 (CTCAE-4) guideline represented in Table 1.

Statistical analysis

Eventually, the obtained data were entered into the Statistical Package for the Social Sciences (SPSS) version 24. The descriptive data were presented in mean, standard deviation, median, percentages, and absolute numbers. For analytics, Mann-Whitney, Fisher's exact test, and chi-square were utilized. To estimate the survival Kaplan-Meier curve and Cox regression were used. In addition, *P* value of less than 0.05 is considered a significant level.

Results

Patient characteristic

Among the 51 patients assessed for eligibility to participate in the study, 45 met the inclusion criteria. The excluded cases have consisted of two persons older than 65 years old, a person with the altered diagnosis from AML to myelogenous dysplastic syndrome, a person with raised liver function tests, and a person with chronic kidney disease (Figure 1). In the current study, the numbers of 45 patients with a median age of 34 years (range: 16-59 years) were assessed. Most of the study population was male (68.9% versus 31.1%), and the most prevalent type of hematologic disorder in them was AML (55.6%) followed by B-cell ALL (33.3%), T-cell ALL (8.9%), and undifferentiated leukemia (2.2%), respectively. The primary chemotherapy regimen of 19 ones was hyper-CVAD (42.2%) and remained 26 ones (57.8%) were primarily treated with a 7+3 regimen. Complete remission was observed in 66.7% of the studied patients, while 33.3% of them never experienced remission. The median duration of remission was six months, with a range of 0-15 months.

The primary salvage chemotherapy regimen of 23 patients was FLANG (51.1%), while 22 ones (48.9%) were treated with mitoxantrone plus etoposide. In the second salvage therapy, 6 (50%) underwent FLANG therapy and 6 (50%) underwent mitoxantrone plus etoposide therapy. The demographic information and primary salvage regimen of the two assessed groups are presented in detail in Table 2. Based on this table, the two assessed groups were similar in terms of demographics ($P>0.05$).

Complete remission was achieved in 47.8% of those under FLANG salvage therapy and 50% of the rater group ($P=0.87$). Grade 4 type of chemotherapy toxicity was the most common type in both of the regimens ($P=0.22$). The mortality rate in the FLANG treated group was 95.7%, among which 72.7% died due to the underlying malignancy, 22.7% due to chemotherapy-related complications, and 4.5% for other reasons. In the latter group, death occurred in 73.7% of the patients, among which 73.7% died because of their malignancy and 26.3% for the adverse effects of chemotherapy (Table 3).

Progression-free survival analysis

The Kaplan-Meier assessments of progression-free survival among the patients of the two assessed groups are shown in Table 4. The mean of progression-free survival was more in the FLANG treated group as compared with the mitoxantrone plus etoposide group, while the Breslow test represented an insignificant difference between the two groups ($P=0.38$). Figure 2 demonstrates the progression-free survival in the two assessed groups of the study.

Discussion

Leukemia relapse/refraction continues to be a significant challenge for hematologists. Even by the emergence of novel salvage regimens, those with relapsed leukemia would not survive for a long time. Another significant issue for the hematologist is to administer a salvage

Table 1. CTCAE-4 guideline for the chemotherapy-related toxicity

Adverse Event	Blood and lymphatic system disorders				
	Grade				
	1	2	3	4	5
Febrile neutropenia	-	-	ANC <1000/mm³ with a single temperature of >38.3 degrees C (101-degree F) or a sustained temperature of ≥ 38 degrees C (100.4-degrees F) for more than one hour.	Life-threatening consequences; urgent interventions indicated.	Death

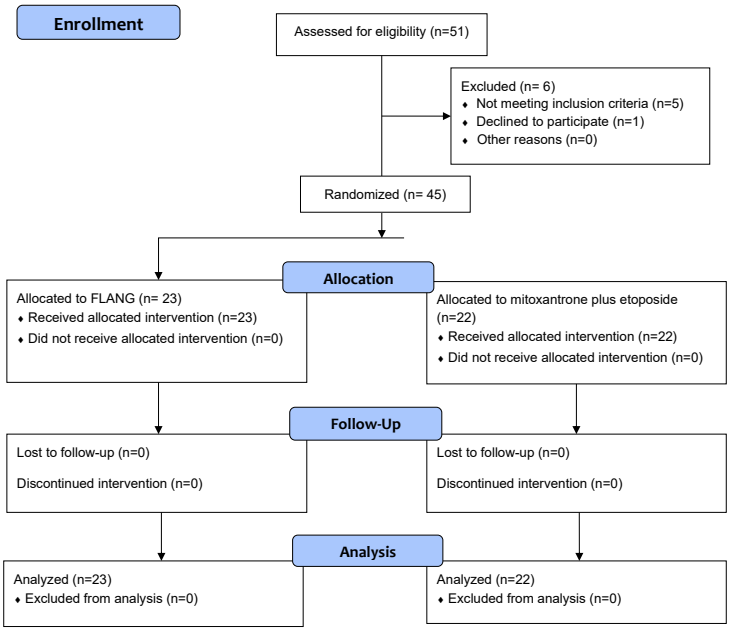

Figure 1. The consort diagram of the studied population.

regimen that induces an elongated complete remission to provide appropriate healthy conditions for allogeneic hematopoietic stem-cell transplantation. Therefore, studies aiming to find the most efficacious salvage regimen with the least adverse effects are in progress worldwide (12,13).

Although cytarabine based combination therapies play the primary role for the salvage regimens used for relapsed/refractory leukemia, since a long time ago, the combination of mitoxantrone and etoposide have been found useful for patients with refractory/relapsed non-M3 AML (14,15), even up to 61% of complete remission has been represented by the use of this combination therapy for relapsed AML (16). We found a considerable high complete remission rate of 50% following the use of mitoxantrone plus etoposide for our patients, while unfortunately, progression-free survival was not remarkable in our study population. In a recent study by Im et al conducted on 91 patients with the first course of relapsed AML, they represented a complete remission rate of 25% with a median event-free survival duration of 12 months (7). Attempts have been made to make better responses considering complete remission achievement, more prolonged overall survival, and less toxicity due to the use of lower doses of cytotoxic agents (17). Cytarabine is a highly effective cytotoxic agent used for both induction and consolidation treatment of AML, while its addition to usual salvage regimens does not have a steep history (17). Trifilio et al conducted a study assessing the addition of cytarabine to the combination of mitoxantrone plus etoposide for refractory/relapsed cases of AML and represented considerable improved mean complete remission rate of 59% versus the mean rate of mitoxantrone plus etoposide that accounted for 34%, however, the overall survival did not improve significantly (18). Liedtke et al, conducted another study on 40 patients with refractory/relapsed ALL patients using the mentioned regimen in combination with cytarabine 1000 mg/m^2/day in a ten-year retrospective study and represented an average complete remission rate of 30% with a median duration of 11.2 months (19).

The latter assessed regimen of our study was FLANG

Table 2. Demographic information, type of primary regimen, remission occurrence, and refractory/relapsed nature of leukemia in the study population

Variable	Salvage chemotherapy regimen		*P* value
	FLANG (n = 23)	Mitoxantrone plus etoposide (n = 22)	
Age, median (IQR)	33 (24-43)	47.5 (23-52)	0.25*
Gender, n (%)			
Female	4 (17.4)	10 (45.5)	0.052**
Male	19 (82.6)	12 (54.5)	
Type of cancer, n (%)			
ALL (B-cell)	9 (39.1)	6 (27.3)	0.49#
AML	12 (52.2)	13 (59.1)	
ALL (T-cell)	1 (4.3)	3 (13.6)	
Undifferentiated leukemia	1 (4.3)	0 (0)	
An induction chemotherapy regimen, n (%)			
Hyper-CVAD	10 (43.5)	9 (40.9)	0.86**
7+3	13 (56.5)	13 (59.1)	
Remission, n (%)			
No remission	8 (34.8)	7 (31.8)	0.83**
Complete remission	15 (65.2)	15 (68.2)	
Refractory/relapsed, n (%)			
Primary refractory	8 (34.8)	7 (31.8)	0.83**
Relapsed	15 (65.2)	15 (68.2)	
Duration of remission, median (IQR)	7 (0-8)	4 (0-8.25)	0.81*

IQR, interquartile range.
* Mann-Whitney; ** Chi-square; # Fisher's exact test.

Table 3. Comparison of response rate, chemotherapy-induced toxicity, and mortality among the refractory/relapsed leukemia patients under either FLANG or mitoxantrone plus etoposide treatment

Variable	Salvage chemotherapy regimen		*P* value
	FLANG (n=23)	Mitoxantrone plus etoposide (n=22)	
The primary response to salvage therapy, n (%)			
Complete regimen	11 (47.8%)	11 (50%)	0.87*
Partial regimen	2 (8.7%)	1 (4.5%)	
Early death	2 (8.7%)	3 (13.6%)	
No remission	8 (34.8%)	7 (31.8)	
Chemotherapy-induced hematologic toxicity, n (%)			
Grade 2	1 (4.3%)	5 (22.7%)	0.22*
Grade 3	5 (21.7%)	6 (27.3%)	
Grade 4	13 (56.5%)	7 (31.8%)	
Grade 5	4 (17.4%)	4 (18.2%)	
Mortality, n (%)			
Yes	22 (95.7%)	19 (86.4%)	0.26*
No	1 (4.3%)	3 (13.6%)	
Etiology of death, n (%)			
Underlying malignancy	16 (72.7%)	14 (73.7%)	0.98*
Chemotherapy-related complications	5 (22.7%)	5 (26.3%)	
Others	1 (4.6%)	0 (0%)	

*Fisher's exact test.

Table 4. Kaplan-Meier results of progression-free survival in patients with relapsed/refractory acute leukemia treated with FLANG or mitoxantrone plus etoposide

Progression-free survival	Mean			Median			*P* value[a]
	Estimate	SE	CI	Estimate	SE	CI	
FLANG	5.87	2.45	(1.065, 10.674)	4	0.440	(3.138, 4.862)	0.38
Mitoxantrone plus etoposide	4	1.074	(1.895, 6.105)	3	0.624	(1.777, 4.223)	

CI, Confidence interval;SE, Standard error.
[a]Log-rank test.

that induced complete remission in 47.8% of the cases. The most prevalent type of toxicity found among these patients was life-threatening consequences requiring urgent interventions. This regimen was administered by Luo et al for 45 patients with refractory AML. They represented 51% of complete remission, event-free survival of 10 months. Nausea, vomiting, bleeding, hyperbilirubinemia, renal toxicity, and arrhythmia were the most common chemotherapy-induced adverse effects presented by patients, while cerebral hemorrhage, hematological toxicity, and pulmonary infection were the most prominent complications of the FLANG regimen in their study (20). Another report by Hänel et al, on 29 refractory/relapsed AML patients showed acceptable response rates, including 59% of complete remission, and 3.2 months of event-free survival. They represented neutropenia and thrombocytopenia as the most common adverse effect elongated for 21 and 23 days, respectively. The most common life-threatening adverse effect of the FLANG regimen was a neutropenic infection. Besides, another prominent complication of their cases was pulmonary dysfunction presented by a patient (21). The complete remission and event-free survival of the patients in the study of Eom et al, on 27 refractory/relapsed AML patients was 56%, and 2.8 months, respectively. Similar to other reports, myelosuppression was the most common complication leading to death in three cases (11%) because of infection due to myelosuppression. The other complication of FLANG salvage treatment was cardiotoxicity in 15% of the patients that required medical interventions (10).

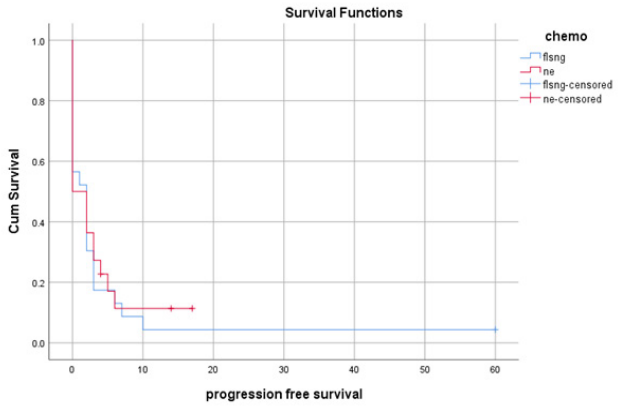

Figure 2. Kaplan-Meier figure of progression-free survival in patients with relapsed/refractory acute leukemia treated with FLANG or mitoxantrone plus etoposide.

The primary manifestation of the current study was to compare the efficacy of mitoxantrone plus etoposide versus FALNG regimen for the treatment of refractory/relapsed acute leukemia cases for the first time. Participants of the two assessed groups were similar in terms of demographic information including age, gender, type of acute leukemia, and clinical findings, including the type of induction therapy, response to induction therapy, refractory/relapsed acute leukemia, and duration of remission following the induction therapy. Therefore, the role of variables probably affecting the outcomes of the study was eliminated. The comparison of the two regimens showed a similar response rate to the salvage remedies. Besides, although type 4 of toxicity was significantly higher among FLANG-treated patients, the general assessment of toxicity induced by the salvage regimens was insignificantly different. Further assessments of progression-free survival revealed similar outcomes for both regimens.

Conclusion

Based on this study, the two salvage regimens of mitoxantrone plus etoposide and FLANG were similar in terms of complete remission, progression-free survival, and toxicity for the cases with refractory/relapsed acute leukemia. The most significant point in this study is the shorter duration of progression-free survival of our patients representing the significance of further investigations to find the underlying reason for this concerning event in Isfahan, the second large province of Iran. Further studies are strongly recommended.

Limitations of the study

The small sample population and the short period of follow-up are the notifying limitations of this study, Furthermore, more detailed information about the probable confounders affecting the response to the treatment can improve the quality of the study. Another limitation of the current study is the concurrent assessment of AML and ALL, while other investigations of one of the groups merely can provide a better insight about salvage therapies in the future.

Acknowledgements

The authors want to offer their most appreciations to Dr. Ali Safaei who has made lots of effort to prepare the current manuscript.

Authors' contribution

VM, MM, and PF were the principal investigators of the study. VM, MM, and PF were included in preparing the concept and design. VM, MM, and PF revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors of this study declare no conflict of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols(IR.MUI.MED.REC.1398.586). This study has been registered in the Iranian Registry of Clinical Trials (identifier: IRCT20190618043939N1, https://en.irct.ir/trial/40272). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from the hematology/oncology fellowship thesis of Dr. Maryam Mirpourian at this university. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

The study was sponsored by Isfahan University of Medical Sciences (Grant # 398201).

References

1. Yamauchi T. [Treatment of acute myeloid leukemia under relapsed/refractory conditions or in older adults]. Rinsho Ketsueki. 2016;57(10):1934-1943. Japanese. doi: 10.11406/rinketsu.57.1934.
2. Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. N Engl J Med. 2015;373:1136-52. doi: 10.1056/NEJMra1406184.
3. Kell J. Treatment of relapsed acute myeloid leukaemia. Rev Recent Clin Trials. 2006;1:103-11. doi: 10.2174/157488706776876445.
4. Oriol A, Vives S, Hernández-Rivas JM, Tormo M, Heras I, Rivas C, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica. 2010;95:589-96. doi: 10.3324/haematol.2009.014274.
5. Jackson GH. Use of fludarabine in the treatment of acute myeloid leukemia. Hematol J. 2004;5 Suppl 1:S62-7. doi: 10.1038/sj.thj.6200392.
6. Westhus J, Noppeney R, Dührsen U, Hanoun M. FLAG salvage therapy combined with idarubicin in relapsed/refractory acute myeloid leukemia. Leuk Lymphoma. 2019;60:1014-22. doi: 10.1080/10428194.2018.1508670.
7. Im A, Amjad A, Agha M, Raptis A, Hou JZ, Farah R, et al. Mitoxantrone and Etoposide for the Treatment of Acute Myeloid Leukemia Patients in First Relapse. Oncol Res. 2016;24:73-80. doi: 10.3727/096504016X14586627440156.
8. Jackson G, Taylor P, Smith GM, Marcus R, Smith A, Chu P, et al. A multicentre, open, non-comparative phase II study of a combination of fludarabine phosphate, cytarabine and granulocyte colony-stimulating factor in relapsed and refractory acute myeloid leukaemia and de novo refractory anaemia with excess of blasts in transformation. Br J Haematol. 2001;112:127-37. doi: 10.1046/j.1365-2141.2001.02551.x.
9. Min WS, Kim HJ, Choi Y, Jeong HY, Kim CC. Interpretation of interleukin-2 receptor alpha positive cells during induction chemotherapy for adult acute myelogenous leukaemia patients. Hematol Oncol. 2007;25:76-83. doi: 10.1002/hon.807.
10. Eom KS, Min WS, Kim HJ, Cho BS, Choi SM, Lee DG, et al. FLANG salvage chemotherapy is an effective regimen that offers a safe bridge to transplantation for patients with relapsed or refractory acute myeloid leukemia. Med Oncol. 2011;28 Suppl 1:S462-70. doi: 10.1007/s12032-010-9653-6.
11. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol. 2000;18:547-61. doi: 10.1200/JCO.2000.18.3.547.
12. Litzow MR, Othus M, Cripe LD, Gore SD, Lazarus HM, Lee SJ,

et al. Failure of three novel regimens to improve outcome for patients with relapsed or refractory acute myeloid leukaemia: a report from the Eastern Cooperative Oncology Group. Br J Haematol. 2010;148:217-25. doi: 10.1111/j.1365-2141.2009.07917.x.

13. Schlenk RF, Döhner K, Mack S, Stoppel M, Király F, Götze K, et al. Prospective evaluation of allogeneic hematopoietic stem-cell transplantation from matched related and matched unrelated donors in younger adults with high-risk acute myeloid leukemia: German-Austrian trial AMLHD98A. J Clin Oncol. 2010;28:4642-8. doi: 10.1200/JCO.2010.28.6856.
14. O'Brien S, Kantarjian H, Estey E, Koller C, Beran M, McCredie K, et al. Mitoxantrone and high-dose etoposide for patients with relapsed or refractory acute leukemia. Cancer. 1991;68:691-4. doi: 10.1002/1097-0142(19910815)68:4<691::aid-cncr2820680404>3.0.co;2-z.
15. Ho AD, Lipp T, Ehninger G, Illiger HJ, Meyer P, Freund M, et al. Combination of mitoxantrone and etoposide in refractory acute myelogenous leukemia--an active and well-tolerated regimen. J Clin Oncol. 1988;6:213-7. doi: 10.1200/JCO.1988.6.2.213.
16. Paciucci PA, Davis RB, Holland JF, Martelo O, Schiffer CA. Mitoxantrone and constant infusion etoposide for relapsed and refractory acute myelocytic leukemia. Am J Clin Oncol. 1990;13:516-9. doi: 10.1097/00000421-199012000-00013.
17. Kohrt HE, Patel S, Ho M, Owen T, Pollyea DA, Majeti R, et al. Second-line mitoxantrone, etoposide, and cytarabine for acute myeloid leukemia: a single-center experience. Am J Hematol. 2010;85:877-81. doi: 10.1002/ajh.21857.
18. Trifilio SM, Rademaker AW, Newman D, Coyle K, Carlson-Leuer K, Mehta J, et al. Mitoxantrone and etoposide with or without intermediate dose cytarabine for the treatment of primary induction failure or relapsed acute myeloid leukemia. Leuk Res. 2012;36:394-6. doi: 10.1016/j.leukres.2011.10.027.
19. Liedtke M, Dunn T, Dinner S, Coutré SE, Berube C, Gotlib J, et al. Salvage therapy with mitoxantrone, etoposide and cytarabine in relapsed or refractory acute lymphoblastic leukemia. Leuk Res. 2014;38:1441-5. doi: 10.1016/j.leukres.2014.09.018.
20. Luo S, Cai F, Jiang L, Zhang S, Shen Z, Sun L, et al. Clinical study of Mito-FLAG regimen in the treatment of relapsed acute myeloid leukemia. Exp Ther Med. 2013;5:982-986. doi: 10.3892/etm.2013.917.
21. Hänel M, Friedrichsen K, Hänel A, Herbst R, Morgner A, Neser S, et al. Mito-flag as salvage therapy for relapsed and refractory acute myeloid leukemia. Onkologie. 2001;24:356-60. doi: 10.1159/000055107.
22. Giles F, O'Brien S, Cortes J, Verstovsek S, Bueso-Ramos C, Shan J, et al. Outcome of patients with acute myelogenous leukemia after second salvage therapy. Cancer. 2005;104:547-54. doi: 10.1002/cncr.21187.