ORIGINAL ARTICLE

The feasibility of PETHEMA ALL-96 regimen on treatment of patients with acute lymphoid leukemia

Farzaneh Ashrafi[1], Alireza Sadeghi[2], Ali Derakhshandeh[2], Padideh Oghab[2]

[1]Aquired Immunodeficiency Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Hematology-Oncology, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Asparaginase-based treatment regimen for acute lymphocytic leukemia (ALL) is considered as feasible, but there is still a lack of data. In this study, considering the results of other regimen that were not optimum in previous studies. Here, we aimed to investigate the feasibility of PETHEMA ALL-96 treatment regimen. **Materials and Methods:** This is a retrospective feasibility study that was performed in 2019–2021 on 13 patients diagnosed with B-cell ALL. Patients were treated by PETHEMA ALL-96 regimen during induction, consolidation, reinduction, and maintenance phases. Patients were followed for 2 years after initiation of PETHEMA ALL-96 regimen for disease-free survival (DFS) and overall survival (OS) of all patients were evaluated after 2 years. **Results:** Data of 11 patients were analyzed. Within 28 days after treatments, all patients (100%) had no blasts in the bone marrow that was considered as complete remission (CR). The CR rate was 100% within 6 months and 12 months and 81.8% within 2 years after the treatments. Evaluation of OS, CR, and DFS regarding 6, 12, and 24 months showed 100% for all items after 6 and 12 months. After 24 months, the CR was 90.9%, the OS was 81.8% and the DFS was 90.9%. None of the patients died during the induction phase and during the 12 months study. No side effects were observed. **Conclusion:** The PETHEMA ALL-96 had high feasibility and survival rates with no side effects during the study course. It is believed that PETHEMA ALL-96 regimen has beneficial outcomes in young patients with ALL.

Key words: Acute lymphocytic leukemia, chemotherapy, overall survival, PETHEMA acute lymphocytic leukemia-96

How to cite this article: Ashrafi F, Sadeghi A, Derakhshandeh A, Oghab P. The feasibility of PETHEMA ALL-96 regimen on treatment of patients with acute lymphoid leukemia. J Res Med Sci 2023;28:30.

INTRODUCTION

Malignancy is one of the major human health problems and the third leading cause of death worldwide. Acute lymphocytic leukemia (ALL) is a malignancy defined by a 20% increase in lymphoblasts of the bone marrow (BM) and peripheral blood by the World Health Organization classification.[1-3]

The clinical signs of ALL include many cases, some of which are: Fever, signs and symptoms of anemia such as fatigue, paleness, weakness, shortness of breath and palpitations, bleeding, disseminated intravascular coagulation, lymph node enlargement, and also bone pain.[4,5] Malignant cells in ALL are actually lymphoid cells such as lymphoblasts that have stopped growing and dividing in the early stages. This growth arrest occurs due to a disorder in the expression of genes that is itself the result of cross-chromosome shifts, mutations in genes, or changes in the number of chromosomes.[6,7]

The results of some studies have also shown that there may be an association between the prevalence of ALL and the patient's previous malignancies such as Hodgkin's lymphoma, small cell lung cancer, and ovarian cancer. Other studies have been performed

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.jrms_4_22

Address for correspondence: Dr. Padideh Oghab, School of Medicine, Al-zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: oghab.p60@gmail.com

Submitted: 01-Jan-2022; **Revised:** 19-Oct-2022; **Accepted:** 14-Nov-2022; **Published:** 20-Apr-2023

on the effect of genetic mutations and chromosomal mutations.[8,9]

The 5-year survival of ALL patients is about 68.2%. Only 20%–40% of ALL patients recover depending on existing treatment regimens.[10,11] Many therapeutic regimens can be used to treat ALL, including the hypercyclophosphamide, vincristine, adriamycin, and dexamethasone (CVAD) treatment regimen, which includes hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone. Other treatment regimens used include: CALGB 8811, GRAALL-2005, Linker 4-drug, and ALL-216.[12-14] The hyper-CVAD regimen entered the global market in 2000, according to a study by Kantarjian *et al*. this treatment regimen consists of two phases: Dose-intensive and maintenance. The results of this study showed that the rate of complete remission (CR) in patients was 91%, which was higher than previous regimens (91 vs. 75%).[15-17]

The use of asparaginase for treatments of ALL has been investigated in various patients groups.[18,19] Previous studies have indicated that administration of asparaginase is associated with increased remission rates in patients but the most notable point of this issue is the side effects of asparaginase-based regimen.[20] These side effects are secondary to immune system disturbance and include allergic reactions, thrombosis, or pancreatitis. The treatment process of ALL is considered difficult and most oncologists avoid the asparaginase-based treatments but it has also been mentioned that these side effects could be fewer in younger patients but further investigations are required.[21]

PETHEMA (Programa Espan˜ol de Tratamiento en Hematologı×a) is a Spanish group that has introduced different treatments for different types of leukemia. The validity of these treatments has been proven in many studies.[22] Although the treatment outcome of young and middle-aged patients is less successful than that of children, recent studies have shown that the success rate of treatment in these patients with pediatric treatment regimens such as PETHEMA ALL-96 is higher than existing treatment regimens. The treatment regimen used to treat ALL patients in Isfahan hospitals is the hyper-CVAD regimen.[23,24] The extent of complete recovery of this regimen in our patients is not known exactly. Studies have declared that PETHEMA ALL-96 could have better therapeutic results and survival rates compared to other regimens including hyper-CVAD, but few studies have been conducted so far.

As mentioned, the results of hyper-CVAD regimen were not optimum in previous studies. This regimen is also associated with high frequencies of side effects. As a result, we aimed to investigate the feasibility of PETHEMA ALL-96 treatment regimen.

MATERIALS AND METHODS

This is a feasibility study that was performed in 2019–2021 in Seyed-Alshohada hospital affiliated to Isfahan University of Medical Science. The current study was conducted on 13 patients under the age of 40 years, diagnosed with B-cell ALL that were treated with PETHEMA ALL-96 regimen. The study protocol was approved by Research Committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI. MED. REC.1399.969).

The inclusion criteria were age below 40 years, diagnosis of B-cell ALL by hematologist using by immunophenotypic, cytogenic and morphological tests of peripheral blood cells, and BM as well as clinical manifestations, candidates for treatments with PETHEMA ALL-96 regimen. The exclusion criteria were the diagnosis of T-cell ALL, presence of t(9;22), t(1;19), t(4;11) or any other 11q23 rearrangements based on cytogenic studies, positive bcr-abl, white blood cells (WBCs) more than 30000 cells per cubic millimeter of blood, previously initiated antileukemic treatment, having uncontrolled or severe cardiovascular, hepatic or renal disease and having severe psychiatric condition.

Patients entered the study based on the inclusion and exclusion criteria.[23] The study population was selected by the census method due to a low prevalence of the disease that means all eligible patients entered the study. Data regarding age, sex, number of leukocytes, lactate dehydrogenase (LDH), and cytogenic results of patients were collected. Patients received the induction phase of PETHEMA ALL-96 regimen using vincristine 2 mg intravenous (IV) at days 1–8–15–22, daunorubicin 30 mg/m^2 IV at days 1–8–15–22, prednisone 60 mg/m^2 IV/PO at days 1–27 followed by 30 mg/m^2 IV/PO at days 28–35, asparaginase 10000 U/m^2 at days 10–12 and 17–19, cyclophosphamide 1,000 U/m^2 (IV) and 24–26 and IT therapy with methotrexate 15 mg, cytarabine 30 mg, and hydrocortisone 20 mg.

BM samples were taken from patients at days of 14 and 28. The presence of ≤10% of blast cells or hypoplastic BM in the BM results was considered as good response to the therapeutic strategies at day of 14. Complete response was considered as <5% of blasts in BM at day of 28. Minimal residual diseases (MRD) were also considered as positive if a patient had more than 10% blasts within 14 days and more than 5×10^{-4} at the end of consolidation phase.

Consolidation phase was also performed for all patients after 28 days using mercaptopurine 50 mg/m^2 PO, methotrexate 3 g/m^2 IV, etoposide 100 mg/m^2 daily for 2 days, cytarabine 500 mg/m^2/12 h and IT therapy with methotrexate 15 mg, cytarabine 30 mg, and hydrocortisone 20 mg.

Furthermore, consolidation-reinduction phase was initiated until the 6 months after the beginning of treatments. The patients received the following drugs during this phase: Dexamethasone 10 mg/m^2 daily PO or IV, vincristine 1.5 mg/m^2 IV, daunorubicin 30 mg/m^2 IV, cyclophosphamide 600 mg/m^2 daily IV, asparaginase 10000 U/m^2 IV and IT therapy with methotrexate 15 mg, cytarabine 30 mg, and hydrocortisone 20 mg. At the end of this phase, patients underwent BM aspiration and MRD was considered positive in case of more than 5×10^{-4}.

The therapeutic regimen was based on PETHEMA ALL-96 and the drugs are summarized and provided in Table 1.

Table 1: The therapeutic drugs based on Programa Espan˜ol de Tratamiento en Hematologı×a acute lymphocytic leukemia-96

Phase/drug	Administration route	Dosage	Days
Remission induction			
Vincristine	IV	2 mg	1, 8, 15, 22
Daunorubicin	IV	30 mg/m^2	1, 8, 15, 22
Prednisone	IV/PO	60 mg/m^2	1-27
	IV/PO	30 mg/m^2	28-35
Asparaginase	IV	10,000 U/m^2	10-12, 17-19, 24-26
Cyclophosphamide	IV	1000 U/m^2	36
Methotrexate	IT	15 mg	1, 29
Cytarabine	IT	30 mg	1, 29
Hydrocortisone	IT	20 mg	1, 29
Consolidation-1			
Mercaptopurine	PO	50 mg/m^2	1-7
Methotrexate	IV	3 g/m^2	1, 28, 56
Etoposide	IV	100 mg/m^2	14-15, 42-43
Cytarabine	IV	500 mg/m^2/12 h	14-15, 42-43
Methotrexate	IT	15 mg	1, 28, 56
Cytarabine	IT	30 mg	1, 28, 56
Hydrocortisone	IT	20 mg	1, 28, 56
Consolidation-2/reinduction			
Dexamethasone	PO/IV	10 mg/m^2/d	1-14
	PO/IV	5 mg/m^2/d	15-21
Vincristine	IV	1.5 (maximum), 2 mg/m^2	1, 8, 15
Daunorubicin	IV	30 mg/m^2	1, 2, 8, 9
Cyclophosphamide	IV	600 mg/m^2/d	1, 15
Asparaginase	IM/IV	10,000 U/m^2	1-3, 15-17
Methotrexate	IT	15 mg	1, 15
Cytarabine	IT	30 mg	1, 15
Hydrocortisone	IT	20 mg	1, 15
Maintenance			
Maintenance-1+ preinductions (until Week 52)			
Methotrexate	IM	20 mg/m^2/week	
Mercaptopurine	PO	50 mg/m^2/d	
Reinductions (every 4 weeks)			
Vincristine	IV	1.5 (maximum, 2) mg/m^2	1
Prednisone	IV/PO	60 mg/m^2/d	1-7
Asparaginase	IV	20,000 U/m^2	1
Methotrexate	IT	15 mg	1
Cytarabine	IT	30 mg	1
Hydrocortisone	IT	20 mg	1
Maintenance-2 (Weeks 53-104)			
Methotrexate	IM	20 mg/m^2/week	
Mercaptopurine	PO	50 mg/m^2/d	

IV=Intravenous; PO=Orally; IT=Intrathecal; IM=Intramuscular

All patients received maintenance therapies at the end of consolidation-reinduction phase until 2 years after the initiation of treatments.

We also collected any signs of toxicity among patients within the therapeutic period. Side effects of asparaginase-based treatments include pancreatitis, increased blood triglyceride levels, allergic reactions, and reduction in the fibrinogen and thrombosis. Other toxicities included fever, prolonged neutropenia, and opportunistic pathogen such as fungus and bleeding.

Patients were followed for 2 year after initiation of PETHEMA ALL-96 regimen. Disease-free survival (DFS) was defined as the time from diagnosis to failure, relapse, death, or last follow-up. Overall survival (OS) was defined as the time from study entry to death or last follow-up. We measured OS, CR, and DFS after 6, 12, and 24 months.

The obtained data were entered into the Statistical Package for the Social Sciences (SPSS) (version 24, SPSS Inc., Chicago, IL, USA). Quantitative data were reported as mean ± standard deviation and qualitative data as frequency distribution (percentage).

RESULTS

A total number of 13 patients entered this study based on the inclusion criteria. Two patients excluded from the study due to WBCs counts more than 30000 cells per cubic millimeter of blood (n = 1) and death during the 1st week of our study due to COVID-19 infection. Data of 11 patients were analyzed. Our study population consisted of 5 males (45.5%) and 6 females (54.5%) with a mean age of 20.18 ± 5.6 years. We showed that the mean WBC count inpatients was 10181 ± 6209.96 cells per cubic millimeter of blood and WBC equal to 10000 cells was most common in patients (27.3%). The LDH levels of all patients were more than 500 units/L. These data are indicated in Table 2.

We also showed that the cytogenetic analysis of patients was normal in 10 patients (90.9%) and 1 patients had abnormal results (trisomy 8), but this patient did not met the exclusion criterion for abnormal cytogenetic analysis.

The evaluation of BM in patients at day 14 after treatments showed ≤10% of blast cells or hypoplastic BM in all patients that showed good response (100%). Within 28 days after treatments, all patients (100%) had no blasts in BM that was considered as CR. We also observed CR in the consolidation phase of patients. We should note that we evaluated the levels of PT, PTT, INR, lipase, amylase, triglyceride, and fibrinogen before treatments and these items were checked again during asparaginase administrations and afterward. Based on our results, none of the patients had pancreatitis, severe reduction in fibrinogen (<70), thrombosis, and asparaginase-related allergic reactions.

Evaluation of OS, CR, and DFS regarding 6, 12, and 24 months showed 100% for all items after 6 and 12 months. After 24 months, the CR was 90.9%, the OS was 81.8%, and the DFS was 90.9% [Table 3].

None of the patients died during the induction phase and during the 12 months study. We also showed that

Table 2: Demographic data and initial information of patients

Variable	*n* (%)
Age: 15-34	11 (100)
Age (years), mean±SD	20.18±5.6
Gender	
Male	5 (45.5)
Female	6 (54.5)
Performance status (ECOG scale)	
0-1	11 (100)
>1	0
Serum LDH	
Normal	0
Elevated	11 (100)
WBC, mean±SD	10,181.82±6209.96
Karyotype	
Normal	10 (90.9)
Abnormal	1 (9.1)
Induction death	0
CR	
CR1	11 (100)
CR2	11 (100)
Toxicity	
Fibrinogen <70	0
Pancreatitis	0
Thrombosis	0
Severe fever and neutropenia	0
Anti-fungal treatment	0
Slow response	0
Good response	11 (100)
Phenotype	
B-cell	11 (100)
T-cell	0

CR1=CR at the end of the induction phase; CR2=CR at the end of the consolidation phase. CR=Complete remission; SD=Standard deviation; ECOG=Eastern Cooperative Oncology Group; WBC=White blood cell; LDH=Lactate dehydrogenase

Table 3: Evaluation of overall survival, complete remission and disease free survival of patients

Variable	Within 6 months (%)	Within 12 months (%)	Within 2 years (%)
CR	100	100	90.9
OS	100	100	81.8
DFS	100	100	90.9

CR=Complete remission; OS=Overall survival; DFS=Disease free survival

no toxicity (fever, prolonged neutropenia, opportunistic pathogen such as fungus, bleeding, or drug-related side effects) was observed among patients during the study course.

Evaluation of MRD at the end of consolidation-reinduction phase (6 months after treatments initiation) among patients showed two positive cases at the end of consolidation-reinduction phase (one with 50 cells/10000 and one with 70 cells/10000) but the rest of patients ($n = 9$) had no MRD. One of these two patients underwent BM transplantation and was expired due to the complications of transplantations almost 14 months after the chemotherapy treatments. The other case was followed that resulted in negative MRD within the therapeutic period. We should also note that one other case was expired almost 2 years after the initiation of PETHEMA ALL-96 regimen due to COVID-19 pneumonia and recurrent ALL that was nonresponsive to treatments.

DISCUSSION

The use of optimal treatment strategies and chemotherapy regimen for ALL that are associated with least complications and side effects are the main goals of surveys in this area. Therapeutic regimen including PETHEMA ALL-96 and Hyper-CVAD are two most important options for patients with ALL. In the present study, we evaluated the results of PETHEMA ALL-96 regimen on 11 patients with a mean age of 20.18 years (all under 40 years) with the diagnosis of B-cell ALL with WBC level of <30000 cells/m^3 of blood and showed that the CR and DFS rate was 100% within 6 months and 12 months after treatments. We also observed no complications or drug-related side effects in our study population. These data emphasize the effectiveness of PETHEMA ALL-96 regimen in these patients.

Previous studies have been conducted on the efficacy of different regimen and also PETHEMA ALL-96 among various groups. In 2008, Ribera *et al*. compared the results of PETHEMA ALL-96 regimen among adolescents and young adults in Spain. They evaluated 35 adolescents and 46 adults and reported that the OS and DFS rates within the 1st year were more than 97%. They also followed the patients for a mean period of 4.2 years and reported that the 6-year event-free survival and OS were 61% and 69%, respectively, with no differences between adolescents and young adults.[25] These data were also approved in 2020[26] showing that PETHEMA ALL-96 regimen could be an effective therapeutic method in patients with ALL. Our results were consistent with these reports showing the beneficial effects of PETHEMA ALL-96 regimen.

Another study was conducted by Sancho *et al*. in 2007 on 33 patients with Philadelphia chromosome-negative (Ph−) ALL patients with the median age of 65 years. It was indicated that CR was achieved in 57.6% within 2 years and 36.4% of patients expired during the study. The DFS rate was reported 39% within 2 years. At the end, they concluded that the prognosis of elderly Ph − ALL patients was poor and using less intensive induction decreased toxic death, allowing delivery of planned consolidation therapy and increased survival probability.[23] In contrast to these results, the OS and DFS ate of the patients within the 1st year was 100% in our study that could be justified by differences in the study populations.

In 2012, Azadbakht *et al*. performed a survey on 11 adults with newly diagnosed ALL. The patients received Hyper-CVAD regimen and were followed for 1 year. It was reported that OS at 6 and 12 months was 91% and 81%, respectively and DFS at 6 and 12 months was 91% and 60%, respectively. It was also reported that febrile neutropenia was seen in 88% of patients in the induction phase.[27] Comparing our data to these results, we also evaluated same number of patients with similar ages and reported significantly higher OS and DFS rates in patients in our study. Furthermore, we observed no side effects and complications during this study. These result show that using PETHEMA ALL-96 regimen is superior to Hyper-CVAD regimen for young patients.

As mentioned earlier, side effects of asparaginase-based regimen are considered as important issues in treatments of ALL patients. The aim of the present study was to investigate an optimal treatment strategy for ALL patients associated with the least side effects. This study showed that the use of PETHEMA ALL-96 that contains asparaginase had no side effects in young patients with ALL and is a safe and effective regimen. We also compared the results of our study to previous research. A study by Erkut and others in 2018 also compared two PETHEMA ALL-93 and hyper-CVAD regimens for patients with ALL. This study was conducted on 38 patients that were treated with hyper-CVAD and 13 patients treated with PETHEMA ALL-93. It was shown that CR was obtained in 90 and 100% of patients, respectively. The OS and DFS were reported 17.5 and 12.1 months, respectively, for Hyper-CVAD and 18.6 and 12.9 months, respectively, for PETHEMA ALL-93. They showed that the 2-year OS rates for Hyper-CVAD and PETHEMA ALL-93 were 30 and 40%, respectively, and the 2-year DFS rates were 28 and 44%, respectively. On the other hand, more complications and side effects were observed in patients treated with PETHEMA ALL-93 including hepatotoxicity, hypofibrinogenemia, *Aspergillus* infection, and skin rash.[28] These data also show the effectiveness of PETHEMA ALL-93 regimen in ALL patients. As mentioned earlier, no significant side effects related to PETHEMA ALL-96 regimen were observed in the current study. This issue could have high clinical importance.

Based on our data, PETHEMA ALL-96 regimen is associated with better therapeutic results compared to hyper-CVAD and also more tolerable in younger patients. Based on our results, 100% of patients had CR within 1 year that is considered as a successful therapeutic strategy. However, restricted study population and follow-up period were the main limitations of the current study. We suggest that more studies on large populations should be performed to consider the best treatments regimen for these patients.

CONCLUSION

The PETHEMA ALL-96 had high feasibility and survival rates with no side effects during the study course. It is believed that PETHEMA ALL-96 regimen has beneficial outcomes in young patients with ALL. We also suggest that by evaluating the toxicity of this treatment regimen, the usage of asparaginase-based treatments in B-cell ALL patients under 35 years should be considered.

Acknowledgments

We should appreciate the chairman and the staff of Al-Zahra hospital in Isfahan for their contribution to data gathering during this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mueller KT, Maude SL, Porter DL, Frey N, Wood P, Han X, *et al*. Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia. Blood 2017;130:2317-25.
2. Hu Y, Wu Z, Luo Y, Shi J, Yu J, Pu C, *et al*. Potent anti-leukemia activities of chimeric antigen receptor-modified T cells against CD19 in Chinese patients with relapsed/refractory acute lymphocytic leukemia. Clin Cancer Res 2017;23:3297-306.
3. Jha KK, Dutta HS. Mutual information based hybrid model and deep learning for acute lymphocytic leukemia detection in single cell blood smear images. Comput Methods Programs Biomed 2019;179:104987.
4. Badar T, Shetty A, Bueso-Ramos C, Cortes J, Konopleva M, Borthakur G, *et al*. Bone marrow necrosis in acute leukemia: Clinical characteristic and outcome. Am J Hematol 2015;90:769-73.
5. Ching T, Duncan ME, Newman-Eerkes T, McWhorter MM, Tracy JM, Steen MS, *et al*. Analytical evaluation of the clonoSEQ Assay for establishing measurable (minimal) residual disease in acute lymphoblastic leukemia, chronic lymphocytic leukemia, and multiple myeloma. BMC Cancer 2020;20:612.
6. Steiner M, Schneider L, Yillah J, Gerlach K, Kuvardina ON, Meyer A, *et al*. FUSE binding protein 1 (FUBP1) expression is upregulated by T-cell acute lymphocytic leukemia protein 1 (TAL1) and required for efficient erythroid differentiation. PLoS One 2019;14:e0210515.
7. Laosai J, Chamnongthai K. Classification of acute leukemia using medical-knowledge-based morphology and CD marker. Biomed Signal Process Control 2018;44:127-37.
8. Symanski E, Tee Lewis PG, Chen TY, Chan W, Lai D, Ma X. Air toxics and early childhood acute lymphocytic leukemia in Texas, a population based case control study. Environ Health 2016;15:70.
9. Rafiee Zadeh A, Ghadimi K, Mohammadi B, Hatamian H, Naghibi SN, Danaeiniya A. Effects of estrogen and progesterone on different immune cells related to multiple sclerosis. Casp J Neurol Sci 2018;4:83-90.
10. Swaika A, Frank RD, Yang D, Finn LE, Jiang L, Advani P, *et al*. Second primary acute lymphoblastic leukemia in adults: A SEER analysis of incidence and outcomes. Cancer Med 2018;7:499-507.
11. Rafiee Zadeh A, Falahatian M, Alsahebfosoul F. Serum levels of histamine and diamine oxidase in multiple sclerosis. Am J Clin Exp Immunol 2018;7:100-5.
12. Man LM, Morris AL, Keng M. New therapeutic strategies in acute lymphocytic leukemia. Curr Hematol Malig Rep 2017;12:197-206.
13. Papadantonakis N, Advani AS. Recent advances and novel treatment paradigms in acute lymphocytic leukemia. Ther Adv Hematol 2016;7:252-69.
14. Douer D. Efficacy and safety of vincristine sulfate liposome injection in the treatment of adult acute lymphocytic leukemia. Oncologist 2016;21:840-7.
15. 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.
16. Jabbour E, Kantarjian H, Ravandi F, Thomas D, Huang X, Faderl S, *et al*. Combination of hyper-CVAD with Ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: A Single-Centre, phase 2 study. Lancet Oncol 2015;16:1547-55.
17. Fahim M, Rafiee Zadeh A, Shoureshi P, Ghadimi K, Cheshmavar M, Sheikhinia N, *et al*. Alcohol and multiple sclerosis: An immune system-based review. Int J Physiol Pathophysiol Pharmacol 2020;12:58-69.
18. Egler RA, Ahuja SP, Matloub Y. L-asparaginase in the treatment of patients with acute lymphoblastic leukemia. J Pharmacol Pharmacother 2016;7:62-71.
19. Marini BL, Perissinotti AJ, Bixby DL, Brown J, Burke PW. Catalyzing improvements in ALL therapy with asparaginase. Blood Rev 2017;31:328-38.
20. Ali U, Naveed M, Ullah A, Ali K, Shah SA, Fahad S, *et al*. L-asparaginase as a critical component to combat Acute Lymphoblastic Leukaemia (ALL): A novel approach to target ALL. Eur J Pharmacol 2016;771:199-210.
21. Raja RA, Schmiegelow K, Albertsen BK, Prunsild K, Zeller B, Vaitkeviciene G, *et al*. Asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol. Br J Haematol 2014;165:126-33.
22. 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.
23. Sancho JM, Ribera JM, Xicoy B, Morgades M, Oriol A, Tormo M, *et al*. Results of the PETHEMA ALL-96 trial in elderly patients with Philadelphia chromosome-negative acute lymphoblastic leukemia. Eur J Haematol 2007;78:102-10.
24. Rodin G, Deckert A, Tong E, Le LW, Rydall A, Schimmer A, *et al*. Traumatic stress in patients with acute leukemia: A prospective cohort study. Psychooncology 2018;27:515-23.
25. Ribera JM, Oriol A, Sanz MA, Tormo M, Fernández-Abellán P, del Potro E, *et al*. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute

lymphoblastic leukemia with the Programa Español de Tratamiento en Hematología pediatric-based protocol ALL-96. J Clin Oncol 2008;26:1843-9.
26. Ribera JM, Morgades M, Montesinos P, Tormo M, Martínez-Carballeira D, González-Campos J, *et al*. A pediatric regimen for adolescents and young adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: Results of the ALLRE08 PETHEMA trial. Cancer Med 2020;9:2317-29.
27. Azadbakht S, Moeinzadeh F, Mehrzad V, Alamsamimy M, Tazhiby M, Ashrafi F. Evaluating the feasibility of prescribing hyper-CVAD regimen in adult acute lymphoblastic leukemia. J Isfahan Med Sch 2012;30:193.
28. Erkut N, Akidan O, Selim Batur D, Karabacak V, Sonmez M. Comparison between Hyper-CVAD and PETHEMA ALL-93 in adult acute lymphoblastic leukemia: A single-center study. Chemotherapy 2018;63:207-13.