

Evaluation of Central Nervous System Relapse in Adults with Acute Lymphoblastic Leukemia (ALL) Receiving Hyper-CVAD Treatment in Seyyed Al-Shohada Hospital: Isfahan, 2014-2019

Alireza Sadeghi¹, Reyhane Gardashti², Farzaneh Ashrafi¹, Valiollah Mehrzad¹

¹Department of Hematology and Oncology, Isfahan University of Medical Sciences, Isfahan, Iran

²Isfahan University of Medical Sciences, Isfahan, Iran

Corresponding Author: Reyhane Gardashti, Isfahan University of Medical Sciences, Isfahan, Iran
E-mail: r.gardashti@gmail.com

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ABSTRACT

Background: Recurrence of ALL in the central nervous system, CNS Relapse, is known as a poor prognostic factor. Few studies have been performed on the CNS Relapse in adults with ALL. This study aimed to evaluate the recurrence of acute lymphoblastic leukemia in the central nervous system, CNS relapse, in adults with ALL.

Materials and Methods: Seventy newly diagnosed patients with acute lymphoblastic leukemia aged 15 years and older referred to Seyyed Al-Shohada Hospital in Isfahan between 2014 and 2019 were included in this study. All patients treated with the Hyper-CVAD regimen underwent prophylaxis for the central nervous system based on the risk of CNS relapse. All study participants with CNS relapse underwent intrathecal chemotherapy.

Results: The median age of patients was 34 years. Four patients (5.7%) had primary central nervous system involvement. Out of 70 patients receiving Hyper-CVAD regimen, 59 (84.2%) achieved complete remission. Of the 59 patients achieving CR, ten (16.94%) developed CNS relapse.

The median duration of CR before CNS relapse was 21 weeks. Out of 10 patients with CNS relapse, seven (70%) achieved complete remission. Of seven patients achieving CR in the central nervous system, one had a second recurrence in the central nervous system, but finally achieved CNS complete remission. The median survival of patients after CNS relapse was four months. The results also showed that out of 10 patients with CNS relapse, four (40%) survived one year.

Conclusion: This study shows that the prognosis of CNS relapse in adults with ALL has not improved much. Limited studies have been conducted on the recurrence of the central nervous system in adults with acute lymphoblastic leukemia. Therefore, further studies on CNS relapse after complete remission of ALL are required to clarify more details.

Keywords: CNS relapse; Acute lymphoblastic leukemia; Hyper CVAD treatment; One-year survival

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant proliferation of lymphoid precursors in the bone marrow, blood, and extramedullary ¹. The ALL incidence in adults is 1 in 100,000². ALL accounts for

about 15-20% of adult leukemias³. Central nervous system (CNS) involvement at diagnosis time is 5-8% in adults ⁴.

ALL Recurrence in the central nervous system, CNS Relapse, is known as a poor prognostic factor⁵.

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CNS relapse occurs in approximately 30-50% of patients who have undergone complete remission (CR) and have not received adequate CNS prophylaxis⁶.

To our knowledge, few studies have been conducted on the CNS Relapse in adults with ALL.

In Iran, several studies have been conducted on the effect of the Hyper-CVAD regimen in patients with ALL. These studies showed a CR rate between 75.7 and 91.6%⁷⁻¹⁰.

This study was conducted to investigate the recurrence of acute lymphoblastic leukemia in the central nervous system, CNS relapse, in adults with ALL.

MATERIALS AND METHODS

Seventy patients with acute lymphoblastic leukemia, aged 15 years and above, who were referred to Seyed Al-Shohada Hospital in Isfahan between August 2014 and August 2019, were included in this study.

All patients were treated with the Hyper-CVAD regimen. All study participants received central nervous system prophylaxis based on the risk of CNS relapse. Prophylaxis consisted of high-dose chemotherapy combined with intrathecal co-therapy. The details of this treatment regimen are described in another study¹¹.

None of the patients underwent cranial radiotherapy for central nervous system prophylaxis. Complete Remission (CR) is defined as blast cell $\leq 5\%$ in normal bone marrow and normal blood cell count is defined as granulocyte count $\geq 1.5 \times 10^9$ / liter and platelet count $\geq 100 \times 10^9$ / liter⁶.

Cerebrospinal fluid (CSF) was taken to diagnose central nervous system recurrence in suspected patients. Recurrence was suspected based on clinical symptoms, including headache, dizziness, cranial nerve palsy, nausea, and persistent vomiting. If the cerebrospinal fluid was not traumatized and blast cells were seen in the CSF specimen, it was considered as the recurrence of the ALL in the CNS. Moreover, CSF flow cytometry was used to diagnose CNS relapse in some patients. In case of suspected clinical signs and symptoms, including cranial nerve neuropathy, central nervous system imaging, including magnetic resonance imaging (MRI), was used to diagnose CNS relapse^{5,12}. All patients with CNS relapse underwent intrathecal chemotherapy. The details of this chemotherapy are described in another study⁶.

Kaplan-Meier method was used for data analysis.

RESULTS

Seventy newly diagnosed patients with acute lymphoblastic leukemia aged 15 years and older were treated with the Hyper-CVAD regimen. The average age of patients was 34 years.

Four patients (5.7%) had primary central nervous system involvement.

Out of the 70 patients who received this treatment, 59(84.2%) achieved complete remission.

Among the 59 patients who achieved CR, 10 (16.94%) developed CNS relapse.

The median duration of CR before CNS relapse was 21 weeks.

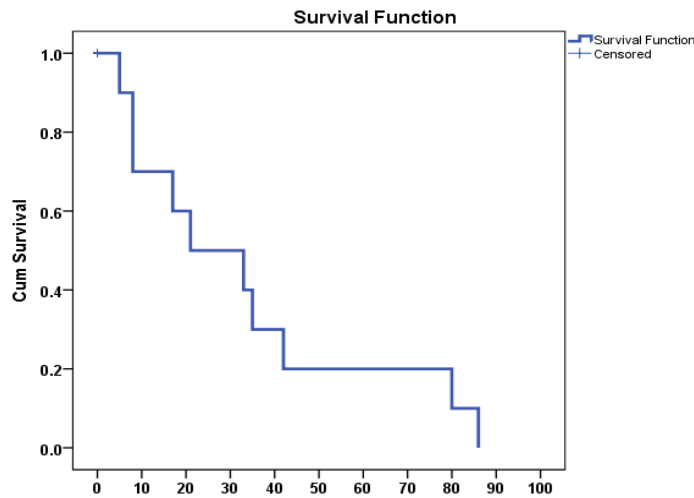


Figure 1. Distribution of survival test data for CNS relapse

The above chart shows the distribution of survival test data for CNS relapse. In this graph, the vertical axis shows the survival rate of the patients with CNS, and the horizontal axis shows the number of weeks that patients were in CR before the CNS relapse. Out of 10 patients with CNS relapse who were treated, seven patients (70%) achieved complete CNS remission.

Of the seven patients who received a CNS CR, one patient had a second CNS recurrence, again achieving complete CNS remission. The average survival of patients after CNS relapse is four months. Moreover, the results showed that out of 10 patients with CNS relapse, four patients (40%) survived until the first year after recurrence in the central nervous system.

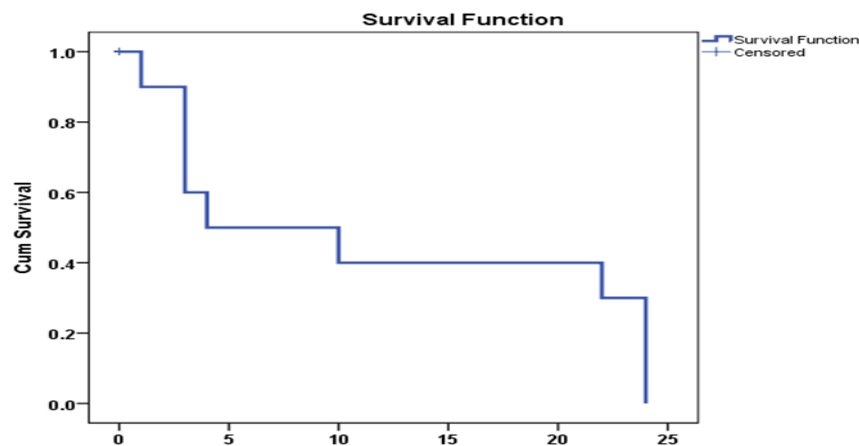


Figure 2. Distribution of survival test data for the survival of patients with CNS relapse

The above diagram shows the distribution of survival test data for the survival of patients with CNS relapse. In this diagram, the vertical axis shows the survival rate of the samples, and the horizontal axis shows the number of months of survival of the patients from the time of CNS relapse during the study period.

Patients were divided into three groups based on the time of CNS relapse^{6,13}.

The first group includes patients who had an ALL recurrence only in the central nervous system (Isolated CNS Relapse). Five patients (50%) were included in this group. The mean time that this group (Isolated CNS relapse) had a complete remission before the CNS relapse was 8 weeks. Two of the five patients later had an ALL recurrence in the bone marrow.

The second group includes patients who had a bone marrow relapse before CNS relapse (CNS relapse after BM relapse). This group included three patients (30%). The average time that patients of this group had CR before recurrence of the ALL in bone marrow was 43 weeks.

The third group included patients with simultaneous recurrence of the CNS and bone marrow (Simultaneous BM and CNS relapse). This group included two patients (20%). The average duration of these patients who had CR before recurrence was 21 weeks.

Finally, the analysis showed a significant difference between the time of recurrence in the three groups (isolated, CNS relapse after BM relapse, and simultaneous BM and CNS relapse) ($P = 0.042$).

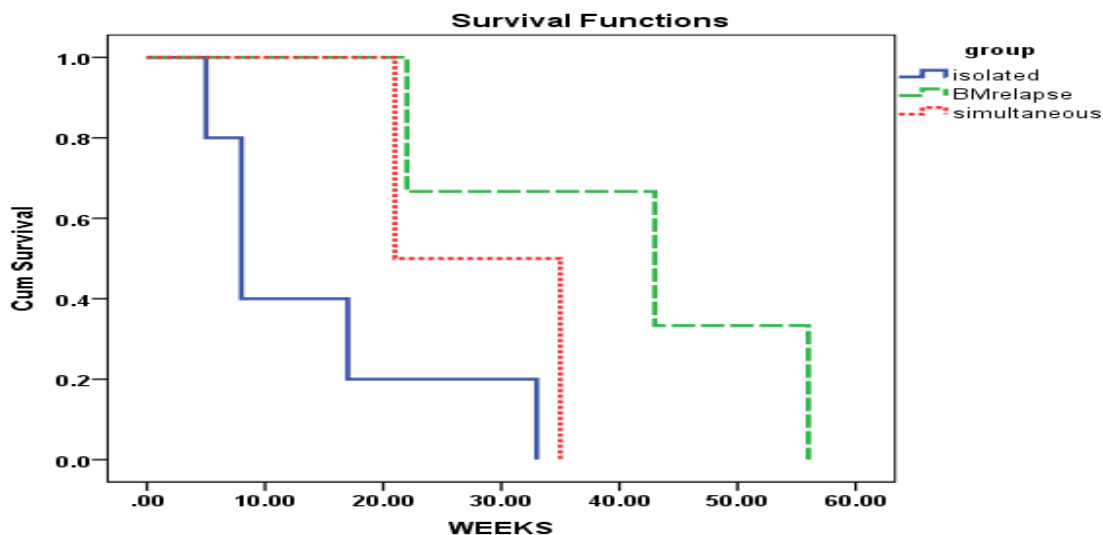


Figure 3. Distribution of survival test data for the time of recurrence in the three groups (isolated, CNS relapse after BM relapse, and simultaneous BM and CNS relapse)

DISCUSSION

This study showed that out of 70 newly diagnosed patients with acute lymphoblastic leukemia treated, 59 patients completely recovered. Among these 59 patients with CR, 10 patients (16.94%) had a recurrence of central nervous system disease (CNS relapse). These results were different from a UR study. Suprapaneni et al.⁶, which is the largest study to date in our knowledge, showed that among the newly diagnosed patients with acute lymphoblastic leukemia treated and had CR, 7% had a recurrence of the ALL in the central nervous system⁶.

In our study, the average CR duration of CNS relapse was 21 weeks. These results are different from the study of Suprapaneni et al. In the study of Suprapaneni et al., the average time that patients had CR before CNS relapse was 36 weeks⁶.

Patients were divided into three groups based on the time of recurrence of the disease in the central nervous system^{6,13}. The first group included patients with disease recurrence only in the central nervous system. The second group included patients who had a bone marrow recurrence before CNS relapse. The third group consisted of patients whose disease relapsed simultaneously in the central nervous system and bone marrow.

According to the results of our study, the average time that the first group (Isolated CNS relapse) had complete remission before the CNS relapse was 8 weeks. This time was shorter than the average time of the second group, (CNS relapse after BM relapse) had complete remission before the disease recurrence in the bone marrow, and the average time of the third group (Simultaneous CNS and BM relapse) had complete remission before recurrence. In contrast, the average time in which the second group had complete remission before the bone marrow recurrence was longer than the median time in which the other two groups had complete remission before ALL recurrence in the central nervous system. This comparison is similar to Suprapaneni et al. study⁶. Finally, compared to other studies, this study showed a lower effect of CNS prophylaxis to prevent the recurrence of CNS ALL, which may be due to the smaller sample size of this study.

Our study showed a higher rate of CNS relapse compared to the study of Suprapaneni et al. There is a possible reason that makes the difference; it is that some risk factors of patients may not be evaluated in our study and they might be responsible for the difference in recurrence rate.

CONCLUSION

This study shows that the prognosis of CNS relapse in adults with ALL has not improved much.

There are limited studies of CNS relapse in adults with acute lymphoblastic leukemia. Therefore, further studies on CNS relapse after complete remission of ALL are needed to clarify more details.

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