RESEARCH ARTICLE

DOI: 10.4274/tjh.galenos.2022.2021.0680
Turk J Hematol 2022;39:152-159

Prophylactic Central Nervous System Irradiation Is Not Indispensable in Adult Patients with Acute Lymphoblastic Leukemia: A Multicenter Retrospective Cohort Study

Akut Lenfoblastik Lösemili Erişkin Hastalarda Profilaktik Santral Sinir Sistemi Işınlaması Vazgeçilmez Değildir: Çok Merkezli Retrospektif Kohort Çalışması

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Abstract

Objective: Studies comparing the efficacy and safety of prophylactic regimens for central nervous system (CNS) involvement in acute lymphoblastic leukemia (ALL) are scarce in adults. This multicenter retrospective study aimed to compare the efficacy of prophylactic regimens with and without CNS irradiation on the development of CNS relapse during follow-up.

Materials and Methods: This was a multicenter comparative cohort study. A total of 203 patients were included from four tertiary care centers in Turkey. Patients were divided into two groups according to whether they received CNS irradiation or not. The groups were analyzed retrospectively regarding patient and disease characteristics, with the main focus being CNS relapse.

Results: While 105 patients received chemotherapy-based prophylaxis, 98 patients received additional CNS irradiation. These groups were statistically comparable in terms of demographic characteristics and risk factors for CNS involvement. In the irradiation group, patients were younger and had more stem cell transplants. In a median of 23.8 (11.1-62.4) months, there was no difference between the two groups regarding CNS relapse-free survival (log-rank p=0.787).

Conclusion: Craniospinal irradiation may not be indispensable for every adult patient with ALL, similarly to pediatric patients. It is crucial to avoid the long-term toxicities of radiation, especially in patients with long life expectancy. Craniospinal irradiation may be reserved for therapeutic use in cases of CNS relapse and prophylaxis for some high-risk patients.

Keywords: Craniospinal, Young adults, Radiation toxicity, Central nervous system relapse, Acute lymphoblastic leukemia

Öz

Amaç: Erişkin akut lenfoblastik lösemi (ALL) hastalarında, santral sinir sistemi (SSS) tutulumuna karşı kullanılan profilaktik rejimlerin etkinlik ve güvenliğini karşılaştıran çalışma bulunmamaktadır. Bu çok merkezli retrospektif çalışmada, profilakside SSS ışınlamayı içeren ve içermeyen rejimlerin etkinliklerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışma, karşılaştırmalı retrospektif kohort çalışması olup; Türkiye'de dört farklı üçüncü basamak merkeze başvuran 203 hastayla yapılmıştır. Hastalar, SSS ışınlaması alanlar ve almayanlar olarak iki gruba ayrılmıştır. Gruplar, takipte SSS tutulumu gelişimi temelinde hastaların ve ALL'nin özelliklerine göre karşılaştırılmıştır.

Bulgular: Yüz beş hasta sadece kemoterapi bazlı profilaksi alırken, 98 hasta ek olarak SSS ışınlaması almıştır. SSS ışınlama grubundaki hastaların medyan yaşı daha küçüktür ve kök hücre nakli oranı daha yüksektir. Bunlar haricinde gruplar, demografik özellikler ve SSS tutulumu risk faktörleri açısından benzer dağılım göstermektedir. Medyan 23,8 (11,1-62,4) aylık takipte, SSS tutulumsuz sağkalım açısından iki grup arasında fark saptanmamıştır (log-rank p=0,787).

Sonuç: Pediatrik hastalarda kanıtlandığı gibi erişkin ALL hastalarında da SSS ışınlaması, çok yüksek riskli hastalar dışında profilakside yer almayabilir. Özellikle yüksek yaşam süresi beklenen hastalarda, ışınlamanın nörolojik toksisitesinden kaçınılması da günümüzde amaçlar arasında olmalıdır. Işınlamanın, SSS tutulumu gelişmiş hastalarda terapötik amaçla sınırlandırılması, çok yüksek riskli hastalar dışında iyi bir risk/fayda oranına sahiptir.

Anahtar Sözcükler: Kraniyospinal, Genç erişkinler, Radyasyon toksisitesi, Santral sinir sistemi nüksü, Akut lenfoblastik lösemi

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Received/Geliş tarihi: December 11, 2021
Accepted/Kabul tarihi: April 21, 2022

Introduction

The negative impact of central nervous system (CNS) involvement on prognosis has long been known for lymphoid malignancies such as acute lymphoblastic leukemia (ALL) and some aggressive non-Hodgkin lymphomas [1,2,3]. In ALL, CNS involvement is reported in 3%-10% of cases at the time of diagnosis [4]. Before CNS prophylaxis, CNS relapse accounts for 75% of cases [5,6]. Although this rate is considerably reduced with chemotherapy and radiotherapy-based CNS prophylaxis adapted from experience and studies of pediatric patients, CNS involvement at the initial diagnosis or relapse is still a significant problem with poor prognosis [7]. In addition to insufficient prophylactic effectiveness, the safety problems of radiotherapy for long-term cognitive and other neurological functions, especially in pediatric patients, also negatively affect the outcomes of surviving patients [8].

Although it is not possible to predict the exact risk of CNS involvement, some patients are considered to be at higher risk. Risk factors include disease-related factors such as hyperleukocytosis, lactate dehydrogenase (LDH) level above 1000 U/L, Philadelphia chromosome and t(4;11) positivity, presence of extramedullary involvement [9,10], and treatment-related factors such as a traumatic lumbar puncture [11].

CNS leukemia often develops as leptomeningeal infiltration and is usually diagnosed with the detection of blastic cells in a cerebrospinal fluid sample [12]. CNS leukemia is rapidly progressive and a determinant of survival. Since it may cause long-term sequelae, it is important to diagnose it in the occult state before it manifests clinically. The use of high-dose chemotherapeutics that can cross the blood-brain barrier, intrathecally administered antimetabolites (mainly methotrexate), and radiotherapy with various combinations show effective results with both short- and long-term toxicities [13]. However, studies on optimal prophylaxis in adult patients in terms of efficacy and long-term safety are very limited. The primary purpose of this study is to compare prophylactic cranial irradiation (PCI) and chemotherapy-based approaches used for CNS prophylaxis in adult ALL patients on the basis of effectiveness.

Materials and Methods

Study Design and Data Collection

This is a multicenter comparative cohort study conducted in a retrospective manner. The study sample consisted of patients treated in the tertiary hospitals of Hacettepe University, Erciyes University, Ondokuz Mayıs University, and Ege University in Turkey. Demographic and medical data of the patients were obtained from electronic and hard-copy medical records. Before data collection, approval was obtained from the Hacettepe University Ethics Committee after receiving the necessary permissions from the other participating centers.

Patients and Disease Characteristics

Patients who were admitted to the centers between January 2000 and January 2021 and diagnosed with ALL at adult ages (≥18 years) were included in the study. Since the study was designed to evaluate the effectiveness of prophylaxis modalities, patients with CNS involvement at diagnosis or before receiving prophylactic treatment were excluded from the study. A total of 203 patients who met the criteria were included in the analyses (Figure 1).

The basic demographic data of the patients, ALL subtypes, diagnosis and treatment dates, risk factors for CNS involvement, treatments received, remission status, CNS involvement status, and final status were recorded. Patients were divided into two groups as those who received and did not receive irradiation for CNS prophylaxis. The chemotherapy-based prophylaxis group consisted of patients who received intrathecal antimetabolite drugs (mainly methotrexate, with additional dexamethasone or cytarabine in some cases) in addition to systemic chemotherapy. The group that received additional PCI consisted of patients who received cranial irradiation at some point in their follow-up.

Given the heterogeneity of regimens used for adult ALL, systemic treatments were divided into pediatric-inspired regimens (including L-asparaginase and high-dose vincristine) and others.

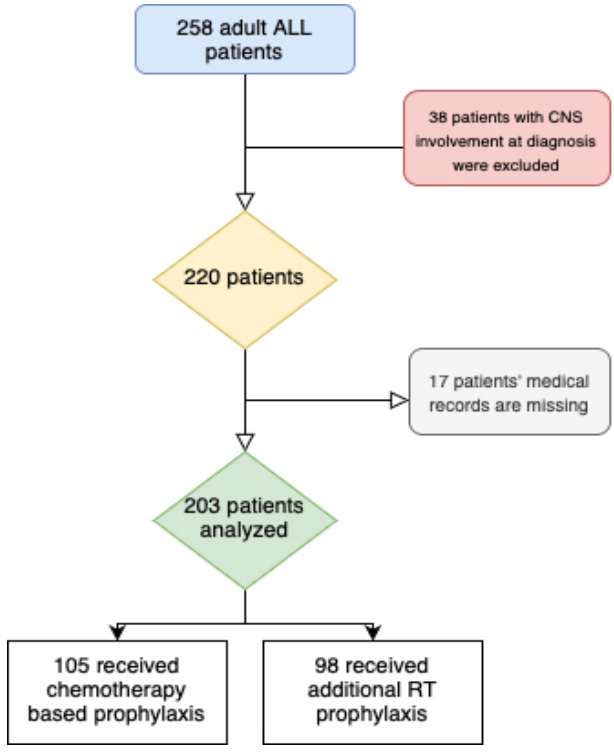

Figure 1. Flow chart of the study.

CNS involvement was defined as the presence of blastic cells in the cytological or flow cytometric examinations of patients' cerebrospinal fluid samples, or pathological positivity in any CNS tissue biopsy, or the presence of high suspicion for leukemic involvement in magnetic resonance imaging in cases of neurological findings that could not be explained otherwise where cytopathological sampling was not possible or diagnostic.

As the main focus of the study, the period from diagnosis to the date of CNS involvement, death, or the last evaluation for surviving patients was defined as central leukemia-free survival (CLFS).

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics 25 for Windows (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods to determine whether they were normally distributed or not. Statistical comparisons were made using chi-square tests for categorical data. The Student t-test for two independent samples was used for the comparison of continuous numerical data. Survival analyses were conducted using the Kaplan-Meier test. Multivariate analyses of predictors of survival were performed using the Cox regression test. Parameters with values of $p \leq 0.10$ in univariate tests were included in the multivariate analysis. Values of $p<0.05$ were considered to indicate statistical significance.

Results

Patient Characteristics

A total of 203 adult patients from four university hospitals were included in the final analyses. The median age at diagnosis was 29.8 (IQR: 22.1-44.7) years and 59.1% of the patients were male. While 98 patients received CNS prophylaxis including irradiation, 105 patients received prophylaxis with intrathecal and systemic CNS-penetrating chemotherapy.

While 152 patients (74.9%) had B-ALL, 49 patients (24.1%) had T-ALL and only 2 (1%) had biphenotypic ALL. Basic demographic data and disease characteristics are shown in Table 1.

During follow-up, CNS relapse occurred in 21 cases. The median time from diagnosis to CNS involvement was 12.1 (4.3-27.7) months and the latest involvement was 36.3 months after diagnosis.

The median follow-up time was 24.54 (IQR: 11.5-63.7) months with a minimum of 1 month and a maximum of 252 months.

Subsequent statistical analyses were performed with two groups according to the treatments used in CNS prophylaxis based on the study's objective. Two arms with and without irradiation were created. Ninety-eight patients received cranial irradiation in addition to systemic and intrathecal chemotherapy for prophylaxis; 105 patients received chemotherapy with systemic and intrathecal administration.

Chemotherapy-Based Versus PCI-Containing Prophylaxis Regimens

Although the treatments received by the patients were heterogeneous in terms of protocols, it was noted that all of them (n=203) received CNS-penetrating systemic drugs, especially high-dose methotrexate.

In the chemotherapy-based group (n=105), the median age was 34.2 (22.6-48.6) years. The patients received a median of 6 (IQR: 4-9) sessions of intrathecal chemotherapy containing methotrexate at doses of 12 to 15 mg. None of the patients who had undergone hematopoietic stem cell transplantation [(HSCT); n=34] received total body irradiation (TBI) in this group. An intravenous busulfan-cyclophosphamide (BuCy) combination was used as the conditioning regimen for the vast majority (n=30, 88%) of transplant patients.

In the PCI group (n=98), the median age was 27.8 (20.3-40.5) years. The patients received a median of 7 (IQR: 4-8) sessions of intrathecal chemotherapy containing methotrexate at doses of 12 to 15 mg and received CNS irradiation at a median dose of 18 Gy (range: 12-24). Fifty-nine patients proceeded to HSCT in this group. Only four of them received Cy-TBI for a conditioning regimen before HSCT at doses of 10-12 Gy irradiation. Eighty-six percent of the HSCT patients (n=51) received BuCy conditioning.

In univariate analyses, the variables of ALL subtype (p=0.927), LDH of >1000 U/L at diagnosis (p=0.07), white blood cell (WBC) count of >1000/µL at diagnosis (p=0.24), allogeneic stem cell transplantation [(ASCT); p=0.29], age at diagnosis (p=0.67), and extramedullary involvement (p=0.12) were not correlated with CNS relapse in our cohort.

Among the variables compared between the prophylaxis groups, ALL subtype (p=0.094), systemic treatment type (p=0.38), LDH level (p=0.5), WBC count at diagnosis (p=0.3), extramedullary involvement (p=0.67), high-risk cytogenetic abnormality (p=0.87), early remission rate (p=0.31), and disease relapse (p=0.38) were not statistically significant in univariate analysis.

Between the two groups, the median age at diagnosis was statistically significantly lower among those receiving PCI (34.2 vs. 27.8, p=0.008). Proceeding to ASCT was also significantly more frequent among those receiving irradiation (60.2% vs. 32.4%, p=0.001).

For CNS involvement, which was the main focus of this study, no significant difference was found between the two groups in terms of CLFS. The Kaplan-Meier curves (log-rank p=0.787)

are shown in Figure 2. CNS involvement occurred in 11 cases in the PCI group and in 10 cases in the chemotherapy-based prophylaxis group. The main features of these cases with CNS involvement are given in Table 2.

Subgroup analyses were performed for the HSCT and non-HSCT groups according to prophylaxis modalities. In the HSCT group (n=93), CNS involvement occurred for nine patients receiving PCI (n=59) and three patients receiving IT chemotherapy only, and this difference was not statistically significant (p=0.373). In the non-HSCT group (n=110), CNS involvement occurred for two patients receiving PCI (n=39) and seven patients receiving IT chemotherapy only (n=71), and this difference was also not statistically significant (p=0.386). The Kaplan-Meier curves for the subgroups are shown in Figure 2.

Discussion

Outcomes and life expectancy in ALL patients have improved with pediatric-inspired treatment regimens, particularly for adolescents and young adults [14]. The introduction of new agents for relapsed or refractory disease has also contributed to overall survival [15,16]. Therefore, reducing the long-term toxicities of treatments and increasing the quality of life, especially in terms of cognitive functions, will also be important goals in the adult ALL population as life expectancy increases with pediatric-inspired regimens for almost all patients.

While some authors suggest that CNS prophylaxis may not be necessary for some very low-risk patients, prospective studies testing this are scarce [17]. Therefore, CNS prophylaxis is currently used as a part of standard therapy for most ALL patients [18].

Table 1. Basic demographic data and disease characteristics of patients.

	CT-only group (n=105)		CT + PCI group (n=98)	
	n	%	n	%
Gender				
Male	61	58.1	59	60.2
Female	44	41.9	39	39.8
ALL subtype				
B-ALL	73	69.5	79	80.6
T-ALL	31	29.5	18	18.4
Biphenotypic	1	1	1	1
CNS involvement in follow-up	10	9.5	11	11.2
Allogeneic HSCT				
Yes	34	32.4	59	60.2
No	71	67.6	39	39.8
Cytogenetic abnormalities				
Philadelphia chromosome	17	16.2	14	14.3
t(4;11)	2	1.9	2	2
t(1;19)	1	1	2	2
t(12;21)	2	1.9	1	1
Negative and others	83	79	79	80.6
Extramedullary involvement at diagnosis				
Yes	19	18.1	15	15.3
No	86	81.9	83	84.7
Systemic chemotherapy regimen				
Pediatric-inspired	61	58.1	82	83.7
Others	44	41.9	16	16.3
Early first remission (<4 weeks)	68	64.7	70	71.4
Median age, years	34.2 (IQR: 22.6-48.6)		27.8 (IQR: 20.3-40.5)	
Median number of IT prophylaxis sessions	6 (IQR: 4-9)		7 (IQR: 4-8)	

ALL: Acute lymphoblastic leukemia, CNS: central nervous system, HSCT: hematopoietic stem cell transplantation, CT: chemotherapy, IT: intrathecal, PCI: prophylactic cranial irradiation, IQR: interquartile range.

Table 2. Main features of cases of CNS involvement among the prophylaxis groups.

	CT-only group (n=10)	CT + PCI group (n=11)
Median IT prophylaxis sessions	5 (IQR: 4-9)	7 (IQR: 6-10)
Median time (months) to CNS involvement	6.65 (IQR: 2.4-16.3)	20 (IQR: 11.3-34.6)
T-ALL phenotype	5	None
Higher risk cytogenetic t(9;22) positivity	1	3
Treatment protocol		
Pediatric-inspired	6	9
Others	4	2
Post-HSCT CNS relapse	3 (Bu/Cy)	9 (8 Bu/Cy, 1 Flu/Bu/ATG)
Medullary disease status		
In morphologic remission	6	4
In relapse/refractory state	3	7
Data missing	1	None

ALL: Acute lymphoblastic leukemia, Bu/Cy: busulfan-cyclophosphamide conditioning, CNS: central nervous system; Flu/Bu/ATG: fludarabine-busulfan and antithymocyte globulin conditioning, HSCT: hematopoietic stem cell transplantation, CT: chemotherapy, IT: intrathecal, PCI: prophylactic cranial irradiation, IQR: interquartile range.

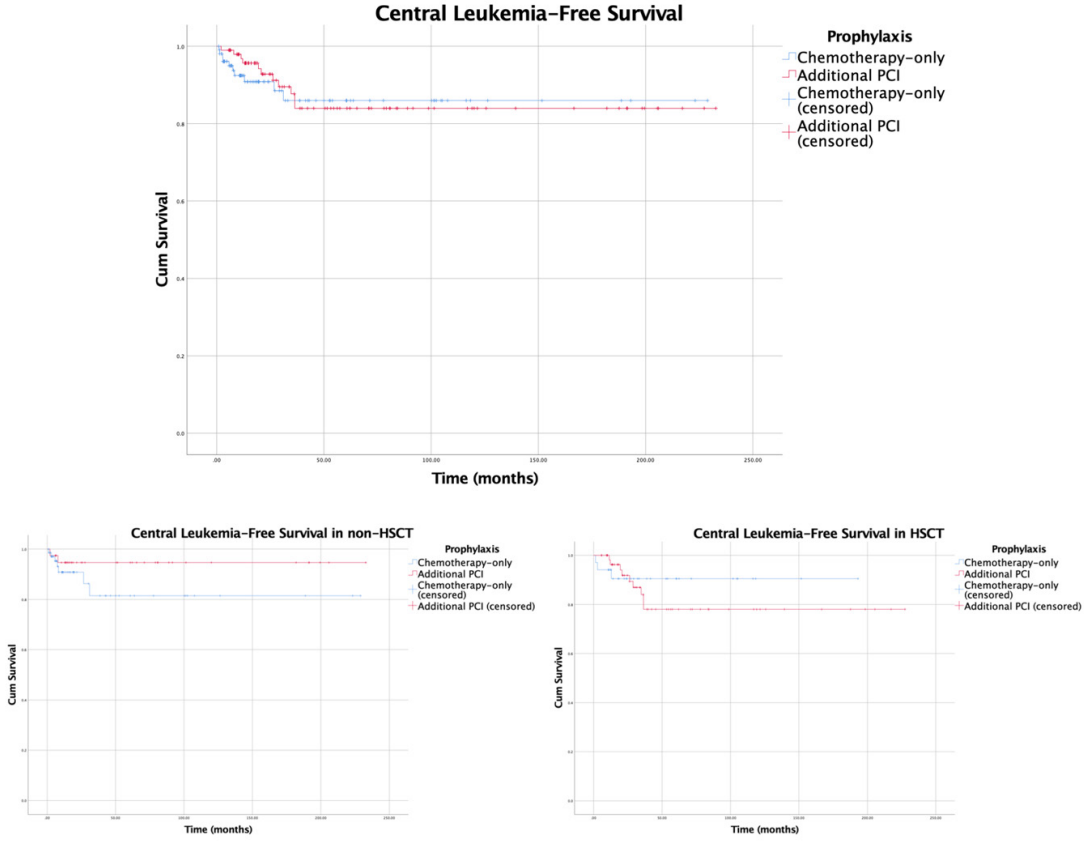

Figure 2. The Kaplan-Meier curves of CLFS for all patients (top) and subgroups (non-HSCT, bottom left; HSCT, bottom right) according to the CNS prophylaxis they received.

CLFS: Central leukemia-free survival, HSCT: hematopoietic stem cell transplantation.

Like any treatment, craniospinal irradiation has both short- and long-term toxicities. Pui and Howard [3] revealed that cranial irradiation increases secondary cancers, neurocognitive deficits, endocrine problems, and growth and development problems in the pediatric population. For these reasons, they stated that prophylaxis was shifted toward intensive intrathecal treatments in addition to systemic therapy. Based on these data and experiences, St. Jude Children's Research Hospital successfully removed PCI from its protocols for all children with newly diagnosed ALL, including those with T-ALL and other high-risk features [19]. While not all of the aforementioned side effects (i.e., those related to growth and development) apply to adults, many of them are potential problems for adults as well as children. In other studies, it has been shown that neurocognitive involvement continues among survivors even decades after childhood leukemia, and there are signs of organic and neurophysiological damage such as early dementia and decreased white matter integrity [8,20,21].

In a study examining whether cranial irradiation has any additional efficacy benefits in chemotherapy-based prophylaxis, it was shown that the risk of CNS involvement and relapse was not increased with regimens without PCI in the pediatric population [13]. There are no well-designed studies in the literature testing this for the adult population. However, based on experiences with primary and metastatic cancers of the CNS, the phenomenon of radiation-induced cognitive decline (RICD) has been defined. Some studies have shown the development of RICD in up to 50% of those who live longer than 6 months after radiotherapy [22,23]. Although the doses and modalities are different compared to other cancers, it can be said that ALL patients who receive prophylactic irradiation will be exposed to more neurocognitive toxicity than those who do not.

Today, combinations of multiple administrations of intrathecal methotrexate in weekly cycles and systemic treatments with central penetrance such as high-dose methotrexate are used for CNS prophylaxis. Although controlled prospective studies are lacking to show the ideal regimen for chemotherapy-based prophylaxis, triple intrathecal drug administration (methotrexate, cytarabine, and dexamethasone) has been shown to reduce CNS involvement and relapse, but not event-free survival, compared to standard methotrexate administration [24]. Newer and longer-acting intrathecal agents such as liposomal cytarabine also promise higher efficacy with fewer administrations [25].

In another study by Jabbour et al. [26], no patient with CNS involvement was observed as a result of the use of intrathecal liposomal cytarabine in combination with systemic chemotherapy containing high-dose methotrexate and cytarabine that was transferred to the CNS during a median follow-up of 7 months, but neurotoxicity increased significantly. In the ALL guidelines of the National Comprehensive Cancer Network, which are widely used around the world, it is recommended that PCI not be applied as a standard except for those with CNS involvement at the time of diagnosis and that irradiation be reserved for therapeutic use in relapsed/refractory cases [27]. Therefore, the use of chemotherapy-based prophylaxis at the right time and dose is also important, and this study has reaffirmed the necessity of interrupting intrathecal treatment during periods when high-dose antimetabolites with CNS penetrance are used.

Considering the guidelines, 98 out of 203 patients in the present study having received PCI seems higher than expected. One of the main reasons for this is that the majority of the patients included in this study received treatment in centers where the necessary personnel and equipment for using conditioning regimens including TBI, which are generally preferred, were not available. Therefore, it is thought that prophylactic irradiation of the CNS at an appropriate point in treatment is used excessively as an effort to reduce the handicap of the lack of TBI.

In the subgroup analyses performed considering the fact that conditioning regimens and graft-versus-leukemia effects may modify the risk of CNS relapse, there were no statistically significant differences between the HSCT and non-HSCT subgroups. These findings suggest that PCI can also be omitted for patients who are not HSCT candidates, except for high-risk patients. However, due to the low event number, these findings need to be confirmed in larger prospective studies. In addition, the rate of CNS involvement being higher in the HSCT subgroup (12 out of 83), although not statistically significant, may have been due to the extended survival and longer time at risk among these patients.

In our cohort, factors such as T-ALL subtype, high LDH level, high WBC count, and extramedullary involvement, which are generally accepted to increase the risk of CNS involvement in the literature, were not associated with an increased risk of CNS relapse. The main reasons for this may be the exclusion of patients with CNS involvement at diagnosis and the small number of patients with CNS relapse in relation to the overall sample size. The median age was significantly lower and the rate of allogeneic HSCT was higher in the PCI group. For aforementioned reasons, PCI was preferred more frequently for patients who were evaluated as HSCT candidates, and HSCT candidates were younger, as expected, accumulating in favor of the PCI group. The lower number of patients who could receive more intensive treatments such as HSCT in the chemoprophylaxis group and the higher median age may explain the early divergence in the Kaplan-Meier curves. Indeed, the curves overlapped after the death of patients at high risk of early mortality.

The major limitations of this study are its retrospective design and sample size. The heterogeneity of the patient, disease, and

therapeutic characteristics of the groups compared stands out as another significant limitation. In addition, the fact that the standard cyclophosphamide-TBI conditioning regimen was rarely applied in the study centers for patients undergoing HSCT may have affected systemic and CNS relapses and may complicate comparisons with other studies in the literature. From another point of view, however, the conditions created by this distinctive situation made it possible to evaluate the effect of prophylactic irradiation on CNS involvement more clearly.

To the best of our knowledge, this is the first study to compare the rates of CNS relapse between CNS irradiation-based and chemotherapy-based regimens for prophylaxis in adult patients. The follow-up periods in the study also seem to have been long enough to assess the risk of CNS involvement.

Conclusion

Based on the data in the literature and experience with the pediatric population, it can be said that CNS irradiation is not indispensable, at least for most adult ALL patients, and especially when high-dose systemic drugs with CNS penetration and intrathecal drugs (mainly methotrexate) are used with sufficient number and duration. In this way, it will be possible to prevent long-term toxicities, especially for adolescents, young adults, and other patients with long life expectancies. Craniospinal irradiation will be able to maintain its place in the prophylaxis of high-risk patients and in the treatment of patients who develop CNS leukemia thanks to its rapid and highly effective properties. However, well-designed randomized controlled trials with long-term follow-up are needed to support this conclusion.

Ethics

Ethics Committee Approval: This study was approved by the Hacettepe University Ethics Committee.

Authorship Contributions

Surgical and Medical Practices: O.E.Ç., H.G., K.F., Ö.A., T.P., Ü.Y.M., M.V., Y.B., S.A., O.İ.Ö., İ.C.H., N.S., F.V., M.T., A.Ü., H.D.; Concept: H.D., H.G.; Design: H.D., H.G., M.T., O.İ.Ö.; Data Collection or Processing: O.E.Ç., K.F., Ö.A., T.P.; Analysis or Interpretation: Ü.Y.M., H.D., Y.B., A.Ü., F.V.; Literature Search: O.E.Ç., N.S., İ.C.H.; Writing: O.E., M.V., S.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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