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Prognostic factors for clinical outcomes of patients with central nervous system leukemia

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Abstract

Prognostic factors associated with clinical outcomes of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) patients with central nervous system (CNS) involvement are unknown. We retrospectively studied the characteristics and outcomes of 66 (18 pediatric and 48 adult) patients with CNS leukemia with ALL ($n = 41$) or AML ($n = 25$). The median age of patients at diagnosis of CNS leukemia was 30 (range, 1–69) years. Nearly two-third patients had CNS involvement at the initial diagnosis of leukemia. Complete remission of CNS leukemia was attained in 58 (88%) patients, and probability of overall survival at 36 months after the diagnosis of CNS leukemia was 43% for the entire cohort. We identified that achieving remission of systemic leukemia and having CNS leukemia diagnosed and treated before allogeneic transplantation were the factors associated with CNS leukemia remission. Prognostic factors associated with better overall survival in patients with CNS leukemia included pediatric age, diagnosis of CNS leukemia before receiving allogenic transplantation, achieving clearance of systemic or CNS leukemia, receiving no cranial radiation in conjunction with intrathecal chemotherapy (IT), and receiving IT consolidation after achieving remission of CNS leukemia.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Our findings show that patients with CNS leukemia are at considerable risk of mortality. Awareness of modifiable prognostic factors such as avoidance of cranial radiation whenever possible and use of IT consolidation can result in improved outcomes in subset of patients with CNS leukemia.

Keywords

CNS; AML; ALL; Leukemia; Prognosis

Introduction

The central nervous system (CNS) is the most common site of extramedullary involvement in adults and children with acute lymphoblastic leukemia (ALL) [1] and is associated with increased risks of morbidity and mortality [2]. CNS involvement is reported in 7% and 3% of patients with ALL and AML, respectively, at the time of initial diagnosis of acute leukemia [3,4] While acceptable long-term survival of 35% has been reported in adult ALL patients with CNS involvement at the time of diagnosis, dismal outcomes were observed in those with recurrence of CNS leukemia after achievement of initial remission [3–5]. Survival of patients with CNS leukemia is particularly poor with AML, with a reported 5-year overall survival (OS) of 11% [6].

The risk factors that predispose patients to CNS leukemia have been studied previously [4,7]. Increased risk of CNS relapse was shown to be correlated with factors such as elevations in alkaline phosphatase, white blood cell count, lactate dehydrogenase, bilirubin, creatinine, fibrinogen, uric acid levels, and circulating blasts [4,7]. However, little is known about factors associated with response to therapy and survival of patients with CNS leukemia. Our goal was to evaluate the risk factors for clinical outcomes of patients with CNS involvement by ALL or AML.

Materials and methods

Patient selection

This retrospective analysis included pediatric and adult ALL or AML patients with CNS leukemia treated at the University of Minnesota from 2007 to 2015. The electronic medical records were queried for patients diagnosed with ALL or AML who had evidence of leukemic blasts by cerebrospinal fluid (CSF) analysis. Blasts were detected by flow cytometric immunophenotyping or by microscopic examination of CSF samples. This study was reviewed and approved by University of Minnesota Institutional Review Board.

Study definitions and endpoints

Reportedly, CNS leukemia was defined as the presence of leukemic blasts in CSF detected by flow cytometry or by cytology [1,8]. Cases of CNS leukemia were classified by timing of CNS involvement in relation to systemic leukemia diagnosis as: (a) CNS involvement at systemic leukemia diagnosis, (b) CNS leukemia between diagnosis of systemic leukemia and hematopoietic cell transplantation (HCT), and (c) CNS relapse post-HCT. Response

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definitions of systemic leukemia were guided by the 2017 European Leukemia Net Recommendations [9]. Complete remission of systemic leukemia (systemic CR) was defined as < 5% bone marrow blasts, absence of circulating blasts or blasts with Auer rods, absence of extramedullary disease, absolute neutrophil count ≥ 1.0×10^9/L, and platelet count ≥ 100×10^9/L. Systemic relapse of leukemia was defined as ≥ 5% bone marrow blasts, or reappearance of blasts in the blood. Complete remission of CNS leukemia (CNS CR) was defined as the absence of blasts in CSF detected by flow cytometry and/or by cytology in two consecutive samples. CNS relapse was defined as recurrence of CNS leukemia after achieving CR detected by flow cytometry and/or cytology.

Statistical analysis

Baseline characteristics and clinical outcome results were obtained from the University of Minnesota prospectively collected Bone Marrow Transplant database. Additional disease-related information was collected from patient electronic medical records. Patient, disease, and transplant characteristics were summarized by standard descriptive statistical methods. Chi-square test was used for statistical comparisons of categorical variables, and Kruskal–Wallis (Wilcoxon) rank-sum test was used for comparisons of continuous variables. Kaplan–Meier method was used to estimate the probabilities of OS after CNS leukemia diagnosis. Univariate comparisons were completed with the log-rank test. Cox proportional hazard regression model was used to estimate differences between the survival curves. Prognostic factor models for all endpoints were created using a backward selection method. The significance level for all p values was 0.05. Statistical analysis was performed with SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Of 66 (18 pediatric and 48 adult) patients with CNS leukemia, two-third patients had ALL and one-third patients had AML (Table 1). Subsequent allogeneic HCT was performed in 40 (61%; 7 pediatric and 33 adult) patients. The median age at acute leukemia diagnosis was 30 years (range, 1–69). All patients with ALL received high-dose methotrexate-based systemic chemotherapy. Systemic CR in the bone marrow and peripheral blood was attained in 54 patients at a median of 44 days after the initial acute leukemia diagnosis. Of these, 24 had systemic leukemia relapse at a median of 294 days after achieving systemic CR. CNS involvement was documented in 43 (63%) patients at the time of the initial leukemia diagnosis, in 16 (24%) patients between the initial diagnosis and receiving HCT, and in seven (11%) patients after HCT. Treatment of CNS leukemia with only intrathecal (IT) chemotherapy was administered in 51 (77%) patients. Eleven (17%) patients received IT chemotherapy in combination with cranial radiation, and the details of therapy were unknown in four (6%) patients. IT chemotherapy included various combinations of methotrexate, cytarabine, hydrocortisone, and cytarabine liposome. Among 52 patients treated at our institution, the median number of IT chemotherapy treatments for each patient was 6 (range, 1–24), and CNS CR was achieved after a median of 2 (range, 1–8) IT treatments. The remaining 14 patients received IT chemotherapy elsewhere; therefore, the

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details on number of IT chemotherapy administered are not available. The median number of consolidation IT treatments received after obtaining CNS CR was 2 (range, 1–21).

Factors associated with first complete remission of CNS leukemia

Overall CNS CR was achieved in 58 (88%) of all patients at a median of 17 days after CNS leukemia diagnosis, of whom 12 (20%) had subsequent CNS relapse at a median time of 199 days after achieving their first CNS CR. Eight patients (12%) had persistent CNS leukemia with no response to any CNS-directed therapy. The probability of CNS CR was higher in patients achieving systemic CR than in those not achieving remission (89% vs. 58%; $p = .01$; Table 2). The rate of CNS CR was also higher in patients with CNS leukemia at initial diagnosis of systemic leukemia or any time prior to HCT than in patients with CNS involvement after HCT (88% vs. 88% vs. 43%; $p = .01$). Patient age, leukemia type, and the type of CNS leukemia therapy had no impact on CNS CR.

Factors associated with survival of patients with CNS leukemia

The probability of 3-year OS was 43% for the entire cohort after CNS leukemia diagnosis (Table 3): 47% if present at initial diagnosis of systemic leukemia, 42% if diagnosed between initial diagnosis and HCT, and 0% if presented after HCT ($p < .01$). Survival was significantly better in pediatric patients than in adults (81% vs. 28%; $p < .01$). As expected, achieving systemic CR resulted in better survival than not achieving systemic CR (51% vs. 8%; $p < .01$). Similarly, while 3-year OS probability was 60% in patients in sustained CNS CR versus 30% in patients with CNS relapse, none of the patients with persistent CNS leukemia survived ($p < .01$; Fig. 1). IT chemotherapy in combination with cranial radiation resulted in worse survival compared with IT chemotherapy alone (18% vs. 51%; $p = .04$). IT consolidation chemotherapy after achieving CNS CR led to improved 3-year OS: 61% versus 53% versus 13% for five or more, one to four, and zero consolidation treatments, respectively ($p = .03$). The median time from CNS leukemia diagnosis to death was 149 (range, 12–1540) days in non-surviving patients.

Discussion

In this analysis of clinical outcomes of CNS leukemia patients with ALL and AML, response to CNS leukemia therapy and OS were not significantly different between patients with ALL and AML. These findings are consistent with a previous report showing similar OS between AML amd AL in pediatric population with relapsed leukemia after HCT [19]. While OS in pediatric patients with CNS leukemia was significantly higher in our study, the likelihood of achieving CNS CR was not significantly different between pediatric and adult patients. Achievement of systemic CR was predictive of achieving CNS CR. Diagnosis with CNS leukemia prior to receiving HCT was also an important factor predictive of CNS CR. Prognostic factors influencing better survival after CNS leukemia included pediatric age, CNS leukemia diagnosis before receiving HCT, achieving systemic CR and CNS CR, receiving IT chemotherapy without cranial radiation, and receiving IT consolidation treatment. In view of the retrospective nature and the single institutional experience of our study, further validation of our findings is warranted in an independent and larger patient cohort. Interestingly, despite similar CNS CR response,

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patients treated with IT chemotherapy without cranial radiation survived better than those who received cranial radiation in conjuncture with IT chemotherapy. An inherent limitation in all retrospective studies—there is only limited information available on why cranial irradiation was considered in some patients. Since the use of cranial radiation as part of initial CNS leukemia therapy and the administration of IT consolidation are modifiable factors, our findings suggest avoid using cranial radiation (e.g., achievement of CNS CR with IT chemotherapy alone) while support using IT consolidation in CNS CR patients whenever possible. We were unable to assess the independent effect of cranial radiation alone on CNS CR or OS since none of the patients in our study received cranial radiation without it being combined with IT chemotherapy. Comparison of cranial radiation versus IT methotrexate for prevention of CNS relapse in a large prospective study for treatment of newly diagnosed ALL in pediatric patients showed similar rates of post-therapy CNS leukemia [10]. While cranial radiation was frequently used in the past for both prophylaxis and initial treatment of CNS leukemia [11], it is being less frequently used nowadays due to reported major long-term neurological complications associated with cranial radiation [12]. However, it may still offer benefits to patients failing to respond to IT chemotherapy [13].

A significantly higher risk of CNS relapse after transplant was previously reported in patients with a prior history of CNS leukemia, where neither the intensity of conditioning regimen nor the post-HCT CNS prophylaxis had significant effect on CNS relapse prevention [14,15]. Another study in 2017 involving ALL patients with CNS leukemia who received HCT using total body irradiation (TBI)-based conditioning followed by prophylactic cranial radiation boost reported decreased risk of post-transplant CNS relapse [16]. Thus, TBI-based conditioning and cranial radiation boost may benefit to patients with a history of CNS leukemia prior to HCT.

Consistent to prior reports, we also observed extremely poor survival of patients with CNS leukemia relapse after HCT [14]. Notably, none of the patients in our study were alive 3 years after diagnosis of CNS leukemia when occurring after HCT. This is likely related to availability of only limited and largely ineffective treatment options for management of relapsed leukemia after HCT [18].

Because standard-of-care therapy options do not benefit patients with post-HCT relapse of CNS leukemia, other strategies are being explored to improve outcomes of these patients. While promising initial results have been reported with use of IT donor lymphocyte infusions for treatment of post-HCT CNS leukemia, this therapeutic approach still remains experimental and should only be used in the context of clinical trials [17]. Strategies focused on prevention of CNS leukemia relapse and treatment of CNS leukemia after HCT warrant further investigation.

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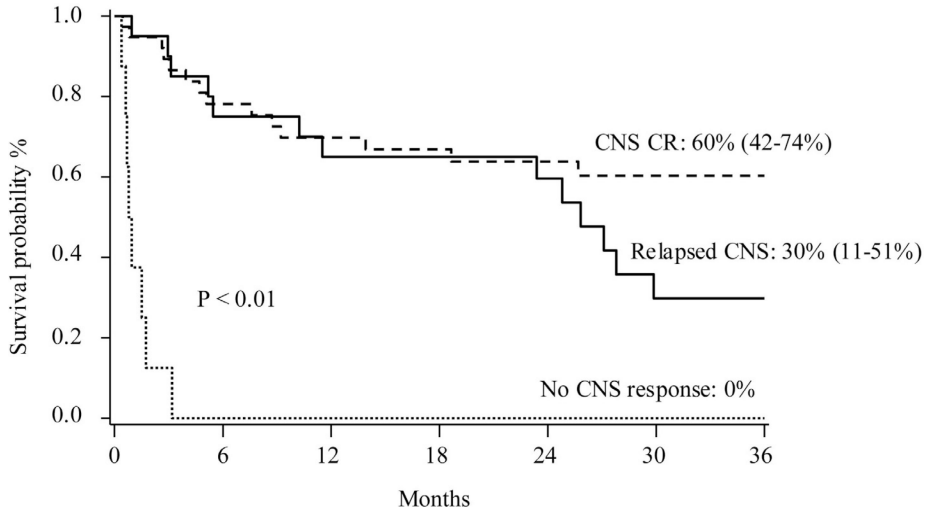

Fig. 1.

Survival probability at 3 years by central nervous system leukemia response. *Note*. CNS = central nervous system; CNS CR = CNS complete remission.

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Table 1

Characteristics of the Study Population.

Variables	Strata	*N* (%)
All patients	66 (100)	
Age at diagnosis	Median (range), yr	30 (1–69)
	≤18	18 (27)
	>18	48 (73)
Sex	Male	37 (56)
	Female	29 (44)
Acute leukemia type	B-cell ALL	32 (48)
	T-cell ALL	9 (14)
	AML	25 (38)
Systemic leukemia response status	CR	54 (82)
	No response	12 (18)
Allogeneic HCT	Yes	40 (61)
	No	26 (39)
CNS Leukemia		
Time of diagnosis	At initial diagnosis	43 (65)
	Between diagnosis and HCT	16 (24)
	After HCT	7 (11)
CNS leukemia therapy type	IT chemotherapy alone	51 (77)
	IT therapy + cranial radiation	11 (17)
	Unknown	4 (6)
IT treatments	Median (range)	6 (0–24)
	N to CNS CR, median (range)	2 (0–8)
	N of consolidation, median (range)	2 (0–21)
Response to CNS treatment	CR	38 (58)
	Relapsed after CR	20 (30)
	No response	8 (12)
Median duration between CNS leukemia diagnosis and death in days (range) (*N* = 36)		149 (12–1540)
Median follow up in days (range)		1275 (28–3277)

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Variables	Strata	*N* (%)
Survival status	Alive	30 (46)
	Dead	36 (54)

Note. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CR = complete remission; CNS = central nervous system; HCT = hematopoietic cell transplantation; IT = intrathecal; N = number.

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Table 2

Central Nervous System Leukemia Response to Therapy.

Variables	Strata	*N*	CNS CR *N* (%)	*p*
All patients		66	58 (88)	
Age at diagnosis, yr	≤18	18	14 (78)	0.46
	>18	48	41 (85)	
Sex	Male	37	30 (81)	0.58
	Female	29	25 (86)	
Leukemia type	B-cell ALL	32	25 (78)	0.54
	T-cell ALL	9	8 (89)	
	AML	25	22 (88)	
Systemic leukemia response status	CR	54	48 (89)	0.01
	No CR	12	7 (58)	
Timing of CNS leukemia	At initial diagnosis	43	38 (88)	0.01
	Between diagnosis and HCT	16	14 (88)	
	After HCT	7	3 (43)	
CNS leukemia therapy type (*N* = 62)	IT chemotherapy alone	51	44 (86)	0.68
	IT therapy + Cranial radiation	11	10 (91)	

Note. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CNS = central nervous system; CNS CR = CNS complete remission; HCT = hematopoietic cell transplantation; IT = intrathecal.

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Table 3

Overall Survival of Patients with Central Nervous System Leukemia.

Variables	Strata	*N*	3-yr OS probability % (95% CI)	*p*
All patients		66	43 (30–55)	
Sex	Men	37	36 (20–52)	0.39
	Women	29	52 (31–69)	
Age at diagnosis, yr	≤18	18	81 (52–94)	<0.01
	>18	48	28 (16–43)	
Leukemia type	AML	25	31 (14–51)	0.29
	B-cell ALL	32	47 (28–65)	
	T-cell ALL	9	56 (20–80)	
Systemic leukemia remission status	CR	54	51 (36–64)	<0.01
	No response	12	8 (1–31)	
Timing of CNS leukemia	At initial diagnosis	43	47 (31–62)	0.01
	Between diagnosis and HCT	16	42 (18–65)	
	After HCT	7	0	
CNS leukemia therapy type (*N* = 62)	IT chemotherapy alone	51	51 (36–64)	0.04
	IT therapy + cranial radiation	11	18 (3–44)	
Number of total IT chemotherapy (*N* = 52)	≤6	25	37 (17–58)	0.37
	>6	27	41 (22–59)	
CNS leukemia response status	CR	38	60 (42–74)	<0.01
	Relapse after CR	20	30 (11–51)	
	No response	8	0	
IT consolidation therapy after CNS CR (*N* = 47)	None	14	13 (1–40)	0.03
	1–4	16	53 (22–77)	
	≥5	17	61 (32–80)	

Note. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CI = confidence interval; CNS = central nervous system; CNS CR = CNS complete remission; HCT = hematopoietic cell transplantation; IT = intrathecal; OS = overall survival.