Original Study

Age Acts as an Adverse Independent Variable for Survival in Acute Lymphoblastic Leukemia: Data From a Cohort in Northeast Mexico

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Abstract

Acute lymphoblastic leukemia is a highly heterogeneous disease whose clinical course and outcome are strongly influenced by age. A cohort including 377 patients of all ages from a low-middle income and homogeneous population receiving standardized treatment protocols over a decade was analyzed. Age < 1 and > 20 years was significantly associated with lower overall survival. Infants fared worst.
Background: Survival for acute lymphoblastic leukemia (ALL) decreases with age. Patients across all age groups from a homogeneous ethnic and socioeconomic background were studied to document age effect. **Material and Methods:** Patients diagnosed from 2005 to 2015 at a university hospital in Northeast Mexico were divided into 4 age groups: infants (< 1), children (≥ 1 to < 16), adolescents (≥ 16 to ≤ 20), and adults (> 20 years). Correlation between age at diagnosis and relapse-free (RFS) and overall survival (OS) was investigated. **Results:** A total of 377 patients were included. Five-year RFS and OS for children were 55.6% and 66.9%; for adolescents, 36.0% and 48.3%; for adults, 19.5% and 24.1%, respectively. Differences in RFS and OS between age groups were significant ($P < .001$, $P < .001$). In the Cox regression model, all age groups reached statistical significance in univariate analysis of mortality. **Conclusion:** Age plays a decisive role in clinical evolution of ALL and strongly influences outcome. Age older than 20 represents a progressive high-risk factor for death.

Introduction

Acute lymphoblastic leukemia (ALL) survival in the pediatric group is approximately 90% in high-income societies,[1] compared with 60% to 70% in Latin American countries.[2-4] For adolescents, progress has been slower, with only modest advances.[5] Adults have the worst prognosis and the slowest progress in survival, irrespective of socioeconomic conditons, with survival at 5 years uniformly less than 50%.[6-8]

There are well-defined factors to assign risk for patients with a new diagnosis of ALL, with age as a significant factor, increasing age

leading to poorer response to therapy and a decrease in survival. The exception are infants youger than 12 months, who represent 2% to 4% of new cases of childhood ALL, who fare less well than children and adolescents, quite similarly to adults, with survival rates ranging from 30% to 50%.[9,10]

Diverse factors drive the divergent outcomes of ALL apart from age, including genetic, biologic, racial, and socioeconomic influences. In low-income groups, drug regimens and drug availability play a notable role. Some factors retain prognostic significance regardless of chemotherapy progress, hematoprogenitor grafting, and application of newer and sophisticated risk criteria.

There are few studies reporting outcomes for cohorts of patients with ALL that include all age groups from the same population in a long-term follow-up allowing appreciatioin of how age reflects an addition of negative factors leading to inferior outcomes.

We studied the clinical evolution of a homogeneous ethnic and socioeconomic group of patients with ALL in a low-middle income population and report the findings of a 10-year period across all age groups to document the age effect on outcomes and

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| Table 1 | Characteristics of 377 Patients With Acute Lymphoblastic Leukemia Diagnosed Between 2005 and 2015 in a Single Center in Monterrey, Mexico |

	Age, y			
	<1	≥1-≤15	16-20	≥21
Characteristics	n (%)	n (%)	n (%)	n (%)
Patients	12 (3.2)	234 (62.1)	57 (15.1)	74 (19.6)
Age, median (range)	7 mo (2-11)	6 (1-15)	17 (16-20)	39 (21-85)
Gender				
Male	6 (50)	125 (53.4)	40 (70.2)	39 (52.7)
Female	6 (50)	109 (46.6)	17 (29.8)	35 (47.3)
Adenopathy				
Yes	0 (0)	58 (24.8)	12 (21.1)	—
No	12 (100)	176 (75.2)	45 (78.9)	—
Organomegaly				
Yes	6 (50)	85 (36.3)	16 (28.1)	11 (14.9)
No	6 (50)	149 (63.7)	41 (71.9)	63 (85.1)
WBC × 10^9/L at diagnosis				
<50,[a] <30[b]	5 (41.7)	189 (80.8)	35 (61.4)	52 (66.2)
>50, >30	7 (58.3)	45 (19.2)	22 (38.6)	22 (28.4)
Initial CNS involvement				
Present	0 (0)	21 (9)	4 (7)	7 (9.5)
Absent	12 (100)	213 (91)	53 (93)	67 (90.5)
Immunophenotype				
B-cell	12 (100)	222 (94.9)	57 (100)	68 (91.9)
T-cell	0 (0)	12 (5.1)	0 (0)	6 (8.1)
Philadelphia chromosome				
Ph$^+$	0 (0)	4 (1.7)	4 (7)	7 (9.5)
Ph$^-$	12 (100)	230 (98.3)	53 (93)	67 (90.5)
Risk at diagnosis				
High-risk	12 (100)	126 (53.8)	57 (100)	57 (77)
Standard-risk	0	108 (46.2)	0 (0)	17 (23)

Abbreviations: CNS = central nervous system; WBC = white blood cell.
[a]For infants, children, and adolescents, WBC cutoff value was 50,000/μL.
[b]For adults, WBC cutoff value was 30,000/μL.

compare these rates with those currently attained in high-income groups.

Material and Methods

We conducted a retrospective study including patients with ALL of all ages, treated in the Hematology Department of the Dr. José Eleuterio González Hospital in Monterrey, Mexico, from 2005 to 2015 and who had complete information in the clinical file and electronic database. The hospital is a public institution that provides health care for low-income patients in the northeast region of the country. Pertinent clinical and biological variables were documented. Patients were divided into 4 age groups: infants, < 12 months; children, 1 to 15 years; adolescents, 16 to 20 years; and adults, > 20 years.

Diagnosis, Criteria for Response and Relapse

Diagnosis was established by findings in a complete blood count and flow cytometry immunophenotyping. Central nervous system (CNS) infiltration was defined as > 5 lymphoblasts/mm^3 in cerebrospinal fluid. Disease risk for children younger than 16 years was assigned into standard and high-risk groups according to National Cancer Institute risk criteria. Infants were considered to have high-risk ALL; all adolescents were considered as high-risk. Adults 35 years or older, with ≥ 30 × 10^9/L white blood cells (WBCs) for B-cell ALL (B-ALL) and ≥ 100 × 10^9/L for T-cell ALL (T-ALL), CNS and/or testis infiltration, or lack of complete remission within 4 weeks of initiated therapy were considered to have high-risk ALL. Relapse was defined by reemergence of the disease and classified as bone marrow, combined, or extramedullary. Fluorescence in situ hybridization and polymerase chain reaction were used to assess Philadelphia (Ph) chromosome status; minimal residual disease was performed in the minority of patients and thus not included.

Treatment

Patients were treated with Berlin-Frankfurt-Munster modified regimens. The results in our group were documented for infants and children,[11] adolescents,[5] and adults.[8]