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ORIGINAL ARTICLE

Analysis of clinical-biological features of adult acute lymphoblastic leukemia (ALL)

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Abstract

Introducction: *Acute lymphoblastic leukemia (ALL) is a clonal disease characterized by a proliferation of immature cells. In immunophenotypic, cytogenetic and molecular studies, it is a heterogeneous disease with diverse manifestations and prognoses. The treatment is complex and is associated with complications during its course.* **Patients and Methods:** *A prospective study of cohort of patients with ALL. Subjects were recruited consecutively from April 2010 to November 2012 in the Specialties Hospital, IMSS.* **Results:** *We included 29 patients with ALL; of 16 females (55%) and 13 males (45%), 18 (64%) were treated with modified BFM, seven (25%) HiperCVAD, and three (11%) others. In all, 70% achieved complete remission, and 8.5% partial responses. Induction mortality in five patients (17%). Consolidation mortality in three (13%). Relapse 33%, with a mean of eight months (5-16 months), overall survival five months. At 26 months of follow-up, 13 patients (45%) maintained RC. Disease-free survival of 10 months and overall survival of 12 months was observed.* **Conclusion:** *The majority of patients, regardless of risk, reach complete remission. We found that the clinical and biological characteristics showed no significant differences related to the outcome. Immunochemotherapy treatment may improve response.* (Gac Med Mex. 2015;151:136-44)

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Introduction

Acute lymphoblastic leukemia (ALL) is a neoplasm characterized by clonal expansion of immature lymphoid cells (blasts) originating in the bone marrow, where they progressively substitute normal hematopoietic tissue and cause a decrease in the number of normal cells of the three hematopoietic series[1], with blasts even being able to access peripheral blood and generate tissue invasion. According to some reports[2,3], ALL accounts for nearly 77% of all pediatric-age leukemias and for 15% in adults[2,3].

In Mexico, the Malignant Neoplasm Epidemiological record of the Ministry of Health reported in 2001 an acute leukemia incidence of 2/100,000 inhabitants/year in the general population. For ALL, this figure was 1.3-5/100,000 inhabitants/year[4,5]. In the USA, age-adjusted global incidence is 1.5/100,000 inhabitants, with peaks between 2 and 5 years of age and a new peak after 50[6].

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The genesis of acute leukemia is associated with genetic lesions in hematopoietic stem cells, which compromise cell differentiation into B- and T-cells[7]. The lesions are produced in regions of the DNA that are critical for cell growth and differentiation processes (generally affecting proto-oncogenes). The mechanisms by which there areas can become lesioned are very diverse: transduction, point mutations, insertion or amplification, but most frequently, chromosomal translocation. Due to this alteration, an incontrolled growth of a hematopoiesis immature precursor's clone is produced, with the resulting accumulation of these in the bone marrow[2].

Chromosomal translocations activate specific transcription genes, which in many cases control cell differentiation and codify for proteins necessary for transcription[8]. Approximately 25% of B-precursor ALL cases have a fusion in the *TEL-AML1* genes, generated by the (12;21) (p13; q22) translocation[9].

Other alteration is the 9;22 translocation or Philadelphia chromosome, which comprises 20-30% in adults and generates the *BCR-ABL* gene fusion[10,11].

More than 50% of T-cell lymphoblastic leukemia cases have mutations involving *NOTCH1,* a gene that codifies for a membrane receptor that regulates T-cell normal development[12].

Clinical manifestations of patients reflect bone marrow infiltration by blasts and extramedullary infiltration, including anemic, febrile, wasting, hemorrhagiparous syndrome; thrombocytopenia and neutropenia; adenomegalies and hepatosplenomegaly[1].

Risk classification allows for prognosis to be estimated and for the neeed for more intensive treatments to be evaluated. Briefly, standard risk is considered when peripheral blood white blood cell (WBC) count < 30,000 cells/ul, patient age < 30 years and no cytogenetic alterations are detected; and high risk, when peripheral blood WBC count > 30,000 cells/ul, patient age > 30 years and cytogenetic alterations are detected, including t(9;22), t(1;19) or t(4;11)[13].

In 1989, the Study and Treatment of Malignant Hemopathies Program (PETHEMA) established induction therapy for 4 weeks, early consolidation and late consolidation, followed by two years of maintenance therapy as treatment for the *de novo* patient[14-16].

The treatment of ALL has shown improvements over the past 3 decades in the adult population. After a first line of treatment, complete response (CR) ranges from 78 to 93%, with an overall survival (OS) rate of 40-50%[17], although 30% of standard-risk patients and 60% of high-risk patients will relapse[18]. CR duration after a relapse is short, and prognosis for adult patients with ALL who relapse is poor. Patients aged < 30 years with remission for more than 2 years showed better probability of survival compared to those who had early relapse. The results of rescue treatments are not satisfactory[19].

In our Hematology Department at the IMSS CMNO Specialties Hospital, the following protocols are used: BFM (Berlin-Frankfurt-Munster)[20], LARSON[21] and Hyper-CVAD[22-24].

Prognosis in adult patients with ALL is modest and the 5-year OS rate is 27-54%; however, in patients classified as high-risk, this rate is lower[25].

Therefore, the purpose of the present work is to identify clinical and biological characteristics of patients with ALL and to find out the correlation of these with the response to treatment.

Material and methods

This is a prospective cohort study of patients diagnosed with ALL who assisted consecutively to the Hematology Department of the IMSS CMNO Specialties Hospital, from March 2010 to October 2012. Patients older than 16 years, with recent and confirmed diagnosis of ALL were included. Exclusion criteria were: patients with history of other hematological or oncological malignancies, non-candidates to receive chemotherapy, previously treated with chemotherapy and with ALL relapse. Elimination criteria were: patients with immunophenotype report of biphenotypic acute leukemia. The following variables were collected: age, gender, fever, central nervous system (CNS) infiltration, performance status, adenomegalies, hepatomegaly, splenomegaly, circulating WBC numbers, hemoglobin, platelets, lactic dehydrogenase and immunophenotype. Performance status was assessed with the scale designed by the Eastern Cooperative Oncology Group (ECOG)[9] of the USA and validated by the World Health Organization (WHO). Response to treatment was assessed according to Cheson's criteria[26]: CR, CR with incomplete hematologic recovery, partial response (PR) and refractory response. For statistical analysis at its descriptive phase, central tendency (mean, median) and dispersion (standard deviation and minimum-maximum values) measures were employed. At its inferential phase, Fisher's exact test was used and the level of statistical significance was considered significant with a p-value < 0.05.

Ethical aspects were established according to article 17 regulations of the General Health Statute on

Table 1. Clinical characteristics of the 29 patients with ALL

Age, years (Median, minimum-maximum value	32 (17-84)
Gender Female/male (%)	16/13 (55/45)
Organomegaly*	6/29 (21†)
Bleeding	11/29 (38)
Fever	13/29 (30)
Lymphadenopathy	15/29 (52)
ECOG	
1	21 (72)
2	7 (24)
3	1 (4)
CNS infiltration	1/29 (3)
Comorbidity	
Hypertension	3 (14)
Other	2 (10)

*Organomegaly = hepato- or splenomegaly.
†Represented in percentage.

Table 2. Biological characteristics of the 29 patients with ALL

	Patients n (%)
WBC (cells/ul)	
≥ 30,000	14 (48)
≤ 30,000	15 (52)
Platelets (cells/ul)	
≤ 25,000	11 (38)
≥ 25,000	18 (62)
LDH	
Elevated	27 (93)
FAB classification	
L1	5 (17)
L2	24 (83)
Immunophenotype	
Pre-B	26 (89)
Classification of risk	
Standard risk	9 (30)
High risk	20 (70)

LDH: lactic dehydrogenase.

Research for Health. The present study corresponds to a minimum-risk investigation and, hence, patients are not expected to suffer any harm as an immediate or late consequence of the study.

Therefore, this proyect does not require for an informed consent letter to be obtained from the patient, since all information will be obtained via clinical records. As a regulatory requirement, the patient must sign an informed consent for hospitalization, as well as an informed consent for his/her treatment.

Results

Thirty-eight ALL-diagnosed patients were assessed between March 2010 and October 2012. All of them underwent a screening protocol. Out of all 38 patients, 29 were included in the study.

Of these 29 patients, 16 (55%) were women and 13 (45%) were men. Mean age was 32 years, with 12 patients (41.3%) older than 30 years.

Patient demographic and clinical characteristics are described in table 1.

A WBC count > 30,000 cells/ul was found in 48% and > 100,000 cells/ul in 27.5% of patients. Presence of mediastinal mass and testicular infiltration was observed in 2 patients. Biological characteristics are shown in table 2.

Morphological classification according to the FAB (French-American-British) classification system was L2 in 24 patients (88%). Immunophenotype showed that 100% were B-cell, out of which 25 (86%) were pre-B, Calla-positive. Presence of the CD20+ marker was observed in 13 (44.8%) of the 29 patients (Fig. 1).

Risk criteria according to Hoelzer were established based on clinical and biological characteristics[20]. Of all 29 patients, 14 (48%) were standard-risk and 15 (52%), high-risk.

Induction therapy results of are shown in table 3. In 69% of all 29 patients, a CR was obtained, in most cases before week 4; only 2 ocurred after week 4; 7% had PR.

Five patients died during the induction phase. The cause of death was: infection in 2 patients (40%), tumor lysis in 2 patients (40%) and hemorrhagic shock in one patient (20%). All these 5 patients who died belonged to the high-risk group.

A sub-stratification of clinical-biological characteristics was made in order to be able to identify whether these influenced on disease remission (Table 4).

The univariate analysis of clinical and biological characteristics and their relationship with the response to treatment before and after week 4 showed no statistical significance (Table 5).

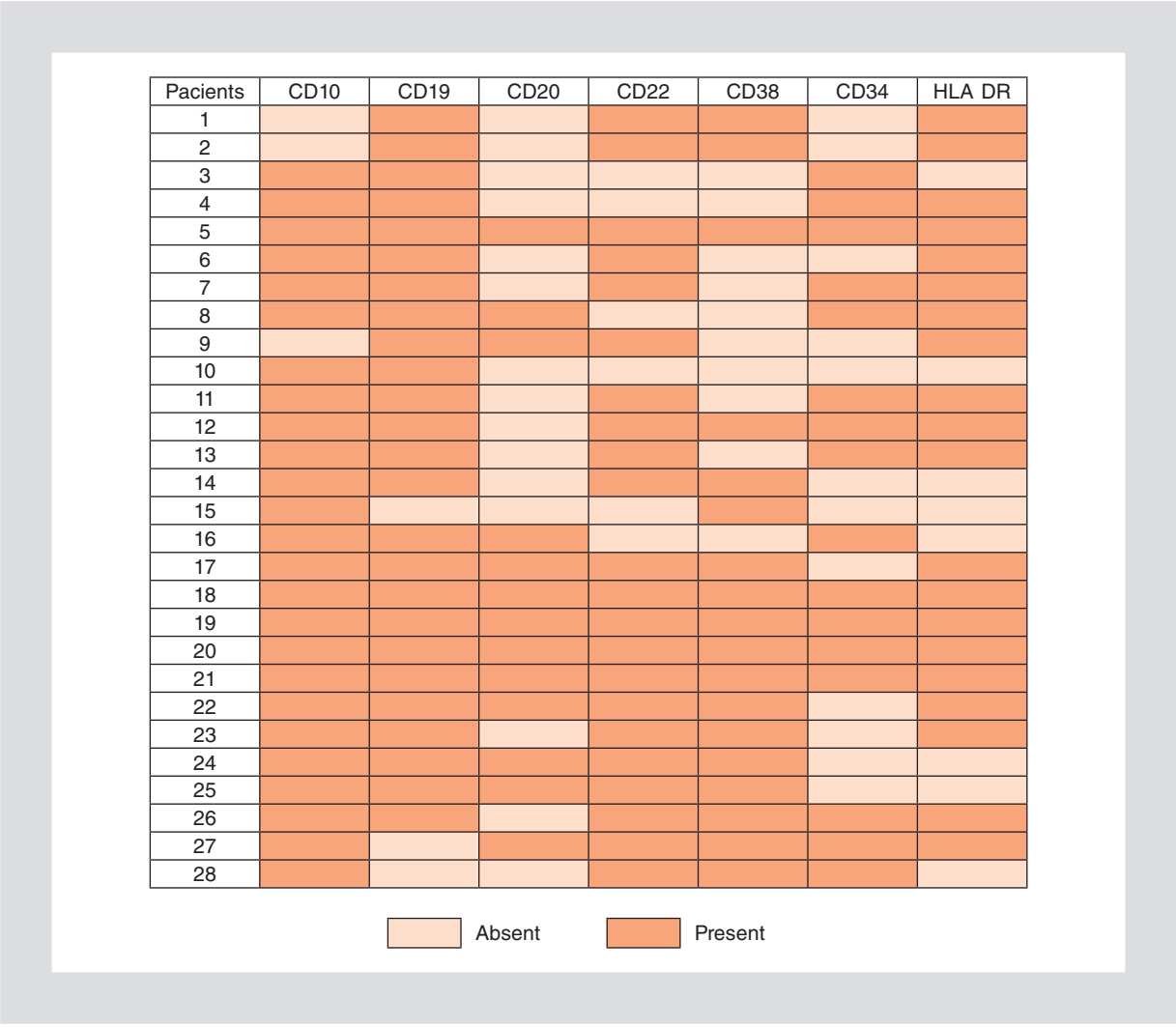

Figure 1. *Immunophenotype of 28 patients with ALL.*

Discussion

The present study of a cohort of adult patients with ALL describes clinical and biological characteristics of the diagnosis of this disease; however, unlike reports from other studies on risk factors, such as Hoelzer reported[20] – CR before week 4, age > 35 years and WBC < 30,000 as prognostic factors –, the result obtained in this study did not show statistical significance for these variables, characterized as high-risk factors.

We found a median age of 32 years. In previous studies in Mexican populations, a median of 31 (18-86)[27] and 27 years (15-65)[28] is reported. Thomas et al.[18] report a median age of 33 years, and Gökbuget et al.[23], a median age of 33 years. In general, the median is 31-34 years of age, ranging from 15 to 81 years.

Of the 29 patients assessed during the 3-year period, immunophenotyping showed that 100% expressed markers for B-cells. During this time, no T-immunophenotype was documented. Ramos et al.[13] report, in 3 years of recruitment, B-markers expression in 67 cases (80%) and only 7 (10%) of T-ALL.

Table 3. Response obtained with the first cycle of treatment

Protocol	Patients (n)	CR	PR
BFM	18	13 (72%)	1 (5%)
Hyper-CVAD	7	5 (71%)	1 (14%)
Other	3	2 (66%)	
None	1		

Table 4. Distribution of frequencies in the sub-stratification of clinical-biological variables

	Patients n (%)
Age	
< 30 years	17 (59)
> 30 years	12 (41)
Adenopathy	
0	14 (48)
1 site	5 (17)
2 sites	8 (28)
3 sites	2 (7)
LDH	
Normal	2 (7)
2 x ULN	15 (52)
3 x ULN	12 (41)
Organomegaly	
0	5 (17)
1	24 (83)
2	
WBC	
< 30,000	14 (48)
> 30,000	7 (24)
> 100,000	8 (28)

*0: no organomegaly; 1: hepatomegaly or splenomegaly; 2: both.

Table 5. Univariate analysis of clinical-biological characteristics in the 29 patients with ALL

	Frequency n (%)	CR n (%)	no CR* n (%)	p
Age				
< 30	17 (59)	14 (82)	3 (18)	0.11
> 30	12 (41)	6 (50)	6 (50)	
Gender				
Male	13 (45)	11 (85)	2 (15)	0.13
Female	16 (55)	9 (56)	7 (44)	
Bleeding				
+	11 (38)	7 (64)	4 (36)	1
–	21 (72)	14 (67)	6 (33)	
Adenopathy				
+	15 (52)	10 (67)	5 (33)	1
–	14 (48)	10 (34)	4 (29)	
Organomegaly				
+	8 (28)	5 (63)	3 (38)	0.68
–	21 (72)	15 (71)	6 (29)	
CNS involvement				
+	1 (3)	0	1 (100)	0.35
–	28 (97)	19 (68)	9 (32)	
LDH				
< ULN	2 (7)	1 (50)	1 (50)	1
≥ ULN	27 (93)	18 (67)	9 (33)	
WBC				
< 300,000/ul	15 (5)	8 (53)	7 (47)	0.25
> 300,000/ul	14 (48)	11 (78)	3 (22)	
CR time				
< 4 weeks	20 (71)	20 (71)	-	-
> 4 weeks	2 (7)	2 (7)	-	
Risk group				
Standard risk	9 (31)	7 (78)	2 (22)	0.68
High risk	20 (69)	13 (65)	7 (35)	

*Includes patients who did not achieve remission and died.

Ruiz-Delgado et al.[27] report on 80 cases (27 females): 92% with B-cell ALL; diploid DNA content, 75%; hyperdiploidy, 20% and hypodiploidy, 5%; CR in 67% and relapse in 25 cases (systemic, 19 cases; in CNS, 6 cases). Arteaga et al.[28] report on 40 cases recruited between 2003 and 2007, with 98% B-cell ALL; CR of 78%, mortality at induction of 2.8%, 11.6-month DFS and 15-month OS; and they find hyperleukocytosis, T-cell immunophenotype and absence of early CR to be related prognostic factors, with a p-value of 0.045, 0.022 and 0.001, respectively[28].

In this population, no cytogenetics studies were performed and, therefore, the presence of the Philadelphia chromosome and how this influences on patients' outcomes (response and relapse) is not known. In a Mexican population, Ruiz-Delgado et al.[27] detected *bcr/abl* in 11 cases (14%), whereas Arteaga-Ortiz[28] reports Philadelphia chromosome in 16.7% of his cases.

In a subgroup of patients, 13 (44.8%) were observed to express the CD20+ marker, which correlates with reports in literature, with 40-50% of all B-precursor ALL cases[29]. The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)[30] demonstrated that CD20 expression had a higher incidence of relapse at 42 months (p = 0.04), which translated into lower DFS (15 vs. 59%) at 42 months (p = 0.003). Thomas et al.,[31] in a phase II clinical trial, demonstrated that the addition of rituximab to Hyper-CVAD improves the results in young patients that express CD20; the rates of durable complete response (DCR) and OS were superior with the Hyper-CVAD + rituximab modification in comparison with standard Hyper-CVAD (70 vs. 38% [p < 0.001] and 75 vs. 47% [p = 0.003], respectively). In this subgroup of patients, it is advisable for monoclonal therapy to be integrated in a protocolized way and for response or outcome variables to be assessed in the medium term.

One patient had infiltration to the CNS at diagnosis – which represents 3% – and died due to tumor lysis.

Reman et al.[32] reported an incidence of 7% (104 of 1,493 patients) for infiltration to the CNS at diagnosis; Lazzarus et al.[33] reported an incidence of CNS infiltration of 5% (77 of 1,508 patients), and Arteaga-Ortiz[28] reported an incidence at diagnosis of 14%. According to the reported studies, patients with infiltration at diagnosis have shown no differences in the attainment of CR versus those without it; however, the incidence of relapse is 8% at 5 years versus 4% in those with no infiltration at diagnosis. Most publications report an incidence of 5-7%, but the incidence was lower in our study population.

In this group of patients, CR was 69.6% with the BFM and Hyper-CVAD regimens, and with the use of cyclophosphamide, doxorubicin, cytarabine and vincristine, 72, 71 and 66%, respectively.

Ramos et al.[13], at the General Hospital of Mexico, over a 3-year period, analyzed 153 patients and reported 63% CR; Thomas et al.[19] reported 72% CR; Ruiz-Delgado[27] reported 67% CR and Arteaga-Ortiz[28], 77% CR. According to reports in literature, our findings are comparable.

In this study we found that the number of patients classified as being at high risk was 20 (69%), out of which 13 (65%) achieved CR. Thomas et al.[19] reported on 429 patients at high risk, out of which 64% achieved CR.

In the univariate analysis, no difference was observed between the standard-risk and the high-risk groups; however, different studies have demonstrated that high-risk patients should receive more intensive chemotherapy treatment and be consolidated with allogeneic transplantation at first CR in order to improve DFS and OS[34].

Mortality at induction was 17.2% (5 patients). Ramos et al.[13] reported a mortality of 20% at induction and Arteaga[28], 2.8% mortality, also at induction. In our population, we found an intermediate mortality with regard to these reports: 2 deaths due to sepsis. In our unit, all patients receive primary prophylaxis with colony-stimulating factor, prophylactic antibiotic therapy and inpatient management in cases of febrile neutropenia and antimicrobial double regimen (cephalosporin + aminoglycoside) and protective isolation. Two deaths due to hemorrhage and one due to tumor lysis syndrome occurred.

Conclusion

Unlike other reports, in our study we found that clinical-biological characteristics showed no significant differences associated with the outcome, probably related to the sample size. Most patients, regardless of the assigned risk, achieved CR; however, these clinical and biological characteristics, as well as response to treatment, are known to have significance on DFS and OS, as well as on the incidence of early relapse, which is why continuous monitoring is advisable in this group.

The best results for outcome variables in ALL are obtained when a risk-stratified treatment is established. Intervention to treatment with monoclonal antibodies can improve the result for outcome variables in a specific group of patients. It is important for the necessary resources to be available for the assessment of biological and molecular characteristics that are reported in literature as being determinant for the design of risk-stratified treatment and, thereby, impact on the response to treatment.

Conflicts of interest and funding source

There are no conflicts of interest and there was no external funding.

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