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ORIGINAL ARTICLE

Long-term destiny of adolescents and young adults with de novo acute lymphoblastic leukemia treated with a pediatric protocol type

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Abstract

Introduction: *The prognosis, in the long term, of adolescents and young adults with acute de novo lymphoblastic leukemia, treated with a pediatric type protocol. Objective: To analyze the efficacy and tolerability of a chemotherapy regimen of pediatric type on patients 15-35 years old with de novo acute lymphoblastic leukemia, Ph(–).* **Methods:** *A retrospective study of patients received from 2001 to 2013, without initial infiltration of the central nervous system. They received the regimen called LALÍN. Terminal goals: frequency of initial remission, probability of survival free of leukemia and event-free survival for five years.* **Results:** *We included 101 patients; there were 29 relapses and 19 deaths. There was initial remission in 97% of the cases; survival free of leukemia of 0.58 and event-free survival 0.44. No difference in patients aged 16-21 years vs. 22-35 (p > 0.55). Negative prognostic factors: abnormal karyotypes, except hyperdiploids (p = 0.001); > 5% of blasts, on 14 day induction (p = 0. 0001); delay in the punctuality of the courses of the chemotherapy regimen (p = 0.0001).* **Conclusion:** *A pediatric type regimen is applicable to patients aged from 16 to 35 years with acute lymphoblastic leukemia, without greater toxicity and a best survival free of leukemia. The count of > 5% of blasts and the delay in the execution of the stages of the chemotherapy regimen are the stronger negative prognostic factors.* (Gac Med Mex. 2016;152:584-90)

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Background

Acute lymphoblastic leukemia (ALL) has a clearly age-related prognosis: in children, it is a relatively controllable disease and, in adolescents, the prognosis is better than in adults and older people. The disease is biologically different at different ages, as recognized since many years ago, which explains the differences in treatment response. This way, immunophenotypes with worse prognosis are more common with increasing age: the T and mature B-cell lineages are predominant in adults[1]. Cytogenetic alterations considered of good prognosis (hyperdiploidies) are more common in children, and those of poor prognosis such as Ph(+), in adults[2].

In the past few years, the need to use intensive, "pediatric-type" chemotherapy (CT) protocols in adolescents and young adults has been emphasized[3-6], in view of better results obtained than with classic, non-intensive, "adult-type" CT protocols.

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In the year 2001, a prospective, comparative study was initiated at the 20 de Noviembre National Medical Center, where patients with ALL from 16 to 21 years of age were included and two regimens were used: LALA for adults (then, subjects older than 15 years) and LALIN, then exclusively employed for subjects younger than 16 years. The results were advantageous for those who received the second regimen[7]. In the year 2007, the decision was made to use the LALIN regimen in 15 to 35-year old patients, based by our results and others reported elsewhere[7-11].

The purpose of this document is to report about our experience with the LALIN protocol in 15 to 35-year old patients. The endpoints are efficacy, as measured according to the frequency of initial complete remission, leukemia-free survival (LFS) and event-free survival (EFS), as well as safety according to the number of deaths occurred during the CT regimen administration.

Patients and methods

This was a longitudinal, descriptive, retrospective, observational study where 16 to 35-year old patients with a diagnosis of de novo ALL according to standard criteria, including more than 20% bone marrow lymphoblasts, attended to at the Hematology Department between January 2007 and December 2013, were included. Data were taken from medical records and from the Hematology Department database. Patients with incomplete medical records or central nervous system (CNS) initial infiltration or Ph(+) were not included. Study variables were the following: age, gender, time of initial evolution, visceromegalies, adenopathies; hematocrit, total leukocytes, platelets, bone marrow blast percentage; cytomorphologic classification according to the French-American-British group; immunophenotype and cytogenetics. All patients were treated with the protocol known as LALIN. The punctuality the CT schedule was complied with was recorded. Final events were recorded: failure, relapse, death (and its cause) or censoring (and its cause). The ultimate goal was to know LFS and EFS.

The LALIN CT regimen or schedule is designed for 15 to 35-year old patients and has been published in detail[7]. It has induction, intensification, consolidation and maintenance phases (Table 1). When initial leukocytes were higher than 50 x 10^9/l, prophylactic radiotherapy was added. Bone marrow blasts were quantified on day 14 of induction phase. Initial remission was looked for on day 28. Elective discontinuation took place at two and a half years, on continuous complete remission.

Definition of terms

- Complete remission: disappearance of all clinical manifestation attributed to the disease. Blood count normalization. Bone marrow: 0-5% blasts, with normal hematopoiesis.
- Failure: more than 5% bone marrow blasts when induction is concluded.
- Myeloid relapse: more than 5% bone marrow blasts with anomalies in the proportion of normal cells, after complete remission is achieved.
- CNS relapse: cerebrospinal fluid blasts on cytology analysis, after disease remission is achieved.
- Extramyeloid relapse: infiltration to organs other than the CNS, demonstrated by histopathology.
- Chemotherapy delay: finalization of the schedule, due to withdrawal, death, relapse or elective discontinuation, occurs after 20% of the projected time.

Statistical analysis

Comparisons were made with the chi-square test (Fisher's or Pearson's) for nominal variables; ANOVA or Kruskall Wallis tests with significance at $p < 0.05$ were used for quantitative variables. Survival tables were calculated with the Kaplan method. Confidence intervals (CI) were calculated at 95%.

Results

One hundred and one patients were included. Male gender frequency doubled that of female gender. Baseline variables are detailed in table 2. Less than half the patients showed splenomegaly or hepatomegaly; in 21 patients, the magnitude of either exceeded 5 cm, and was accompanied by adenomegalies at 2-3 regions in 15 patients. At admission, three mediastinal infiltrations were found (with T-cell lineage), as well as one retinal. Blood blasts mean count was 46% (0-100%), and in bone marrow, 83% (30-100%). L1, L2 and L3 cytomorphologic types were found in 38%, 59% and 4%, respectively. According to the immunophenotype, lineage was of the B (90%) and T (11%) types. In 63 patients, the karyotype showed results: 11 with hyperdiploidy and 9 with hypodiploidy; 5 with translocations different to t (9:22) and one inversion at 9q; the rest were normal, and in 38 it was not analyzed.

In 3 patients (3%) there was no initial complete response. Table 3 shows treatment general results. The sites of relapse were the following: myeloid in 26 cases

Table 1. LALIN CT regimen. IT methotrexate and IT dexamethasone during induction are repeated on day 15. Asparaginase is delivered at 4,000,000 U/m^2, thrice-weekly, from 1.0 to 4.8. Subsequent maintainment (5.1-5.8) is applied until two years on complete, continuous remission are completed

Phase	Drug	mg/m^2/day	Days
1.0	Dexamethasone	10	-4 to 0
	IT methotrexate	12.5	1
	IT dexamethasone	5	1
	Vincristine	2	1, 8, 15, 22
	Daunorubicin	60	0 and 1
	Cyclophosphamide	750	2
	Prednisone	100	1-7 and 15-22
	Asparaginase	4,000,000 U	8, 15, 21, 28
2.0	Cytarabine	3,000	1 to 4
3.1	Methotrexate	1,000	1
	Vincristine	2	1
3.2	Prednisone	180	1 to 7
	Vincristine	2	1
4.1	IT methotrexate	12.5	1, 4, 8, 12
	IT dexamethasone	5	1, 4, 8, 12
4.2	Mercaptopurine	300	1 to 4
4.3	Cyclophosphamide	600	1
4.4	Vincristine	1.5	3
4.5	Prednisone	180	1 to 7
4.6	Methotrexate	650	1
4.7	Daunorubicin	40	1
4.8	Cytarabine	200	3
	Mercaptopurine	100	3
5.1	IT methotrexate	12.5	1
	IT dexamethasone	5	1
5.2	Mercaptopurine	300	1 to 4
5.3	Cyclophosphamide	600	1
5.4	Vincristine	1.5	3
5.5	Predinisone	180	1 to 7
5.6	Methotrexate	650	1
5.7	Daunorubicin	40	1
5.8	Cytarabine	200	3
	Mercaptopurine	100	3

(90%) and CNS in 3 (7%); in one patient it was on the skin, which preceded myeloid relapse by 3 weeks. The causes of death were infection in 14 patients (74%) and hemorrhage in 5 (26%). The distribution of deaths between patients younger than 22 or older than 21 years was similar (p = 0.55). Censoring of patients was due to withdrawal. Only one patient underwent allogeneic transplantation.

The punctuality the CT cycles were administered with was recorded. A total of 871 cycles were administered among all patients. Administration was punctual in 68.3% of cases, and in 31.7% there was delay

Table 2. Baseline characteristics of included patients

Variable	Result
Gender (F/M)	30/71
Age in years, mean (range)	21 (15-35)
Hepatomegaly (n =)	36
Splenomegaly (n =)	34
Weeks of previous evolution, mean (range)	4 (1-25)
Hematocrit %, mean (range)	25 (10-45)
Leukocytes x 10^9/l, mean (range)	61 (0.1-550)
Platelets x 10^9/l, mean (range)	7 (3-810)
Lactate dehydrogenase U/l, mean (range)	877 (112-5,950)
Immunophenotype (B/T)	90/11

Table 3. General results

Result	n =	%
Initial remission*	97	97
No events	46	46
Failure	4	4
Relapse	29	29
Death	19	19
Censored†	3	3

*Complete.
†Withdrawal.

owing to the following causes: myeloid toxicity (with or without infection) in 23 patients, liver toxicity in 5 and administrative reasons in 3.

The likelihood of EFS at 60 months was 0.44 (median of 40 months with a confidence interval of 0.17-0.49). The likelihood of LFS was 0.58. The survival tables are shown in figures 1 and 2. No differences were found in these results when 16 to 21-year old patients were compared with those aged from 22 to 35 years (p = 0.98).

All variables were analyzed looking for facts with predictive meaning. Karyotypes with hypodiploidy, translocation or inversion behaved as negative-prognosis factors (p = 0.001), as well as the presence of more than 5% of bone marrow blasts on day 14 during the induction scheme (p = 0.0001) and the delay on the compliance of the CT schedule (p = 0.0001). The remaining variables had no prognostic value.

Discussion

There are several observations suggesting better treatment results with pediatric-type intensive CT regimens in adolescents and young adults than with those for adults. In addition to known biological adverse factors, fewer opportunities to enter in subsidized protocols, unfavorable psychosocial aspects, economic deprivation and other issues have been described. This has led to insist on creating a specific subset of patients, known as Adolescents and Young Adults (AYAs)[12,13], to address their different characteristics. Specific particularities of patients these ages have to be considered, and not managing them as children or older adults.

AYAs have, indeed, certain biological peculiarities[14]. One of them, from the epidemiological point of view, is the notorious predominance of the male gender; a fact that was noticed since long time ago[15] and that doesn't appear to correspond to bias in the present study. From 1986 to 2014, 931 ALL new cases have been attended to in our department, including 286 children. In patients younger than 15 years, the percentage of female and male gender is 49% and 51%; in 16 to 35-year old patients, 40% and 60%; and in patients older than 35 years, 53% and 47%. In our experience, after 15 and up to 35 years of age, there is a significant predominance of the male gender (p = 0.0005).

In Mexico, CT regimens originally designed for children have been tried in adults[16], with up to 144 months' follow-up, and the probability of LFS has been 35%, but Ph(+) cases were included and some did not receive tyrosine kinase inhibitors because these were not available.

In this report, treatment results at five years, as assessed by the frequency of initial complete remission, LFS and EFS, with no differences found between subjects younger than 22 years and older than 21, are comparable with those reported in other studies[17-19]. They are better than those obtained in a historical control of 53 patients attended to in our department, where an adult protocol was applied, with a 5-year LFS of 34% (p = 0.03). The elevated rate of initial remission is not surprising, and it is a common observation with almost all current protocols. The pediatric-type schemes with intensive CT and few periods of rest have started being used in the course of this century and there are several evidences in favor of their efficacy.

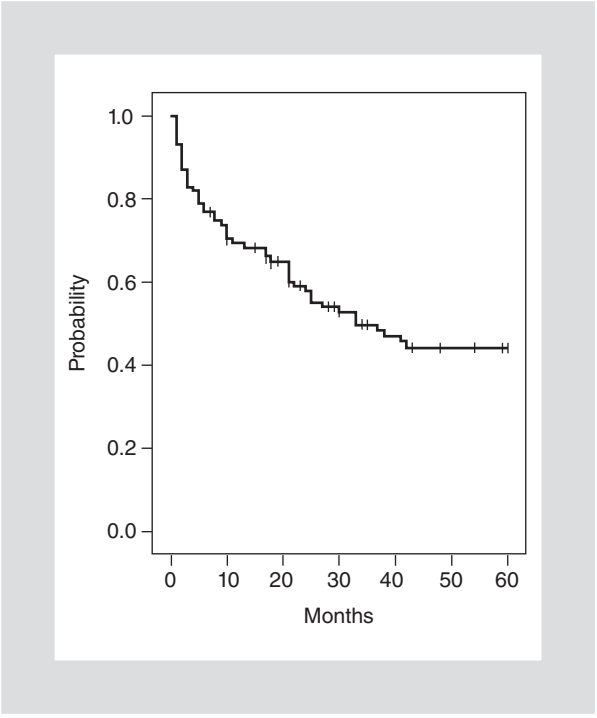

Figure 1. *Probability of EFS at five years.*

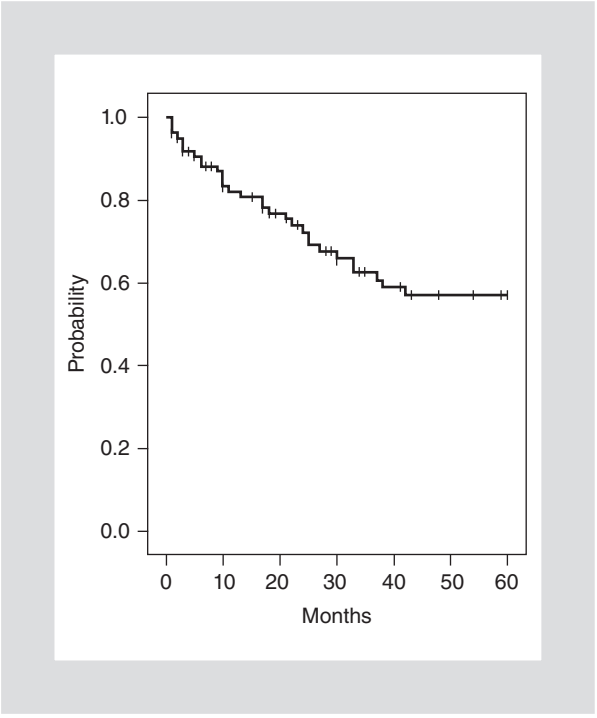

Figure 2. *Probability of LFS at five years.*

There is a thorough meta-analysis[20] that demonstrates this, with studies from different places. Initially, these protocols were applied to adolescents, generally to up to 21-year-old patients, but the limit has been progressively extended up to the vicinity of 35 years, and efficacy has been preserved.

The toxicity associated with these intensive schedules has not been shown to be inacceptable in patients

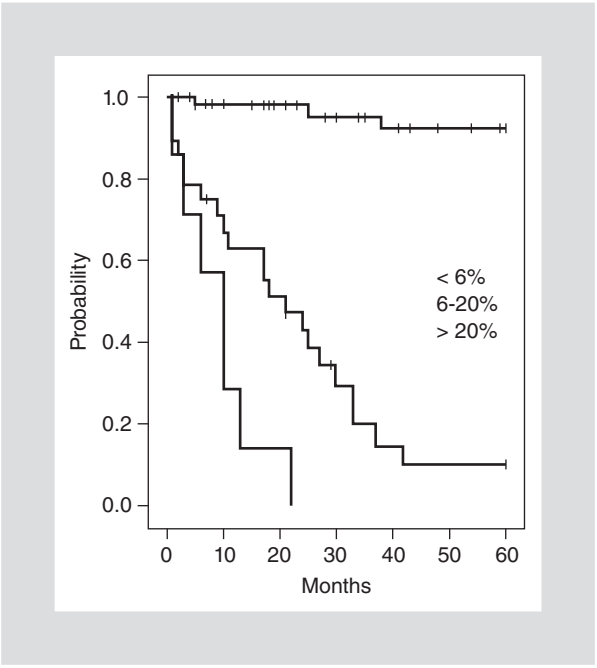

Figure 3. *Probability of LFS at 5 years: influence of the amount of bone marrow blasts on day 14 of induction (p = 0.0001).*

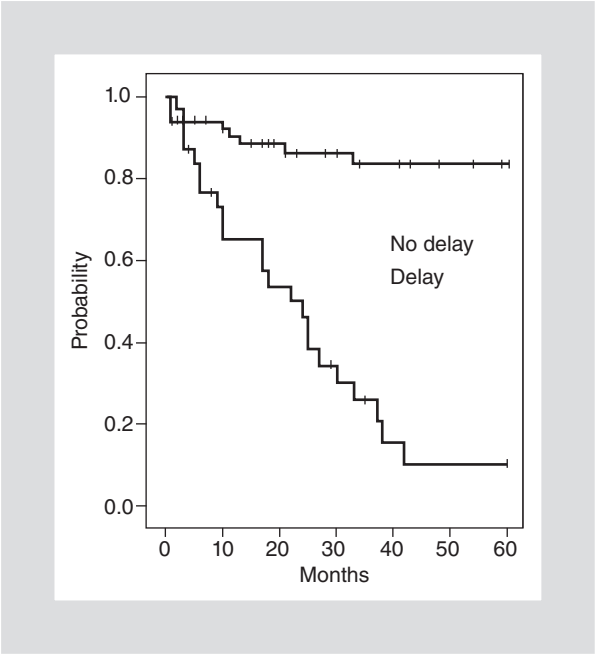

Figure 4. *Probability of LFS at 5 years: influence of treatment schedule delayed punctuality (p = 0.0001).*

older than 21 years. In our study, toxicity, as assessed by the number of deaths itself, was the same in patients older and younger than 21 years. Other previously mentioned studies also report it to be similar.

Their superior efficacy and comparable toxicity have encouraged the use of these protocols in patients older than 35 years. In a systematic review[21], a similar LFS (57%) was found at 3 years in two groups of patients: 14-30 and 31-60 years of age, and toxicity was the same. In an Italian study with 18 to 50-year old patients and a pediatric protocol, 4-year LFS was 69%. There are optimistic opinions, according to which transplantation may turn out being unnecessary in most adolescents and young adults with this new strategy[22]. These facts point at the convenience of applying pediatric-type protocols to patients older than 35 years, a phenomenon that surely will be increasingly common. Nevertheless, it seems unlikely that the results obtained in patients younger than 15 years are going to be attained with the drugs hitherto used for CT. It is necessary to have new compounds with different mechanisms of action available. In this sense, blinatumomab, an antibody that binds to CD19 and CD3-positive cells and starts T cells activation and (CD9-positive) blasts perforin-mediated destruction, has demonstrated very good results in phase I and II trials. By the end of last year, the US Food and Drug Administration approved its use[23].

The immediate purpose of prognostic indicators identification is to stratify the patients in low or high-risk groups. The former have good possibilities of cure with CT and the latter have reasonable possibilities of cure with transplantation at first complete remission[22]. Some prognostic factors can be identified before the treatment is started: age, leukocyte count, immunophenotype and cytogenetics, among others. In a recent report of 353 Ph(-) patients of 18 to 65 years of age, the multivariate analysis identified initial infiltration to the CNS, leukocyte count higher than 30 x 10^9/l and T-cell lineage as poor prognostic factors prior to assessing treatment response[24]. After CT administration, lack of asparaginase in the induction and attainment of initial remission in more than 4 weeks were added. Prior to the start of treatment, we only found negative influence in the karyotype, and after CT initiation we found, as adverse factors, the presence of more than 5% of blasts in the bone marrow on day 14 of induction and the delay in punctuality to apply the CT scheme.

There are different reports indicating similar to the above prognostic data. However, currently, the most appreciated information is the determination of minimal residual disease (MRD)[22]. The methods to determine it are based on the determination of immunophenotypes and immunoglobulin sequences or on the investigation of chromosomal alterations-associated fusion genes. The sensitivity of these methods ranges from 10^{-3} to 10^{-5} (from 0.1 to 0.001%). The efficacy MRD determination is noticed when comparing the 54%-74% rates of LFS if it's positive, with the 17%-40% rates if it's positive. It should be noticed that, unfortunately, 26% or more adult patients will relapse, in spite of negative MRD[22]. Phenotype-based determination is widely used and there are reports indicating that, if assessed at the conclusion of induction and consolidation, it is the only reliable prognostic factor for LFS[25,26]. The most widely used strategy is to continue with CT if there is good response according to MRD; if not, it is preferable proceeding to transplantation[27].

MRD was not determined in our study due to the lack of adequate technology. It was replaced with day 14 blast count. This way of assessing for cytological response has been used since many years ago. We found a negative prognostic value, and highly significant, when the count was higher than 5%. It is an imprecise and inaccurate method when compared with molecular or immunophenotype-based determination, but it is useful since elevated counts are invariably associated with failure or relapse. In contrast, among patients with counts lower than 6%, only 4 relapsed (5%).

We found punctuality in the compliance with the CT schedule to have prognostic value and high statistical weight. It should be taken in account that applying a pediatric-type protocol doesn't only imply changes in CT, but also requires pediatric punctuality. In our cases, we found delays in almost one third of cycles, and unpunctuality was due, in most occasions, to delayed myeloid recovery, in spite of the use of granulocyte colony-stimulating factor. Of the 66 patients with less than 6% of blasts on day 14 of induction, only 15% had delays. Of the 35 cases with more than 5% of blasts, 63% had delays ($p = 0.0001$) (Figs. 3 and 4). This indicates that myeloid recovery velocity during treatment is influenced by initial response to CT.

Conclusion

A pediatric-type CT regimen can be applied to patients with Ph(-) ALL with ages ranging between 16 and 35 years without an increase in toxicity being produced and with a probability of LFS at 5 years of 0.58. A bone marrow blast count higher than 5% on day 14 of induction and the delay on the application

of the CT schedule phases are the two prognostic factors with most weight.

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