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REVIEW ARTICLE

DISEASE-FREE SURVIVAL IN PATIENTS OVER 40 YEARS OF AGE WITH Ph_{NEG} ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH AN INTENSIVE PROTOCOL

***Alvarado Ibarra Martha, Ortiz Zepeda Maricela, Álvarez Vera José Luis, Mena Zepeda Verónica, Espitia Ríos María Eugenia, Jiménez Alvarado Rosa María and López Hernández Manuel**

Servicio de Hematología Centro Médico Nacional "20 de Noviembre". ISSSTE. Ciudad de México. México

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ABSTRACT

Introduction: Despitetheincreasingknowledgeabout acute lymphoblastic leukemia (ALL), the outcome for patients over 40 years of age is not good since they are generally too vulnerable to the toxicity caused by the chemotherapeutic protocols of the "pediatric type".
This group of patients usually tolerates less intensive protocols, but efficacy is diminished in terms of Survival Free of Leukemia.
Objective: To determine the therapeutic results using a local, intensive protocol (LAL10), in patients with Phneg ALL that are older than 40 and are in a condition to receive intensive chemotherapy, treated in the hematology Service of the Centro MédicoNacional "20 de Noviembre" (National Medical Center) in Mexico City.
Patients and Methods: From 2001 to 2015 an intensive chemotherapy program, with curative intent and designated as LAL10, was implemented in a High Specialization Center in Mexico City. The program was directed toward patients older than 40 with a de novo diagnosis of ALL, without an upper age limit. Patients were evaluated after the first dose of chemotherapy. Patients with previous use of anti-cancer agents or Ph+ were excluded. Those who abandoned treatment or went on to HPCT were eliminated.
Results: Eighty-four patients who were in a condition to receive intensive chemotherapywere included. Medium age was 48 years with 26 patients older than 50 (31%). Female patients predominated. The frequency of complete remission was 74 (88%) and 10 patients were refractory. The most frequent event was relapse, constituting 47.6% of cases: 35 in bone marrow, 3 in skin and 2 in central nervous system. The probability for Leukemia-Free Survival to five years was 0.21 with a median of 14 months. The probability of Event-Free Survival was 0.17 with a median of 10 months. There were 32 deaths, 20 of which followed relapse or treatment failure and the other 12 happened between induction and up to the ninth month; the mode was 1 month. There were 7 deaths during induction. Causes of death were infection (24) and hemorrhage (8). The probability of OS at five years was 0.39 with a median of 25 months.
Conclusion: In our experience, relapse was the most frequent event. Although this is not radically different from that observed in other studies on Phneg patients at comparable ages, these results are not considered to be satisfactory, especially when compared to results observed with the AYA group or in those younger than 15. Among the different protocols, chemotherapy usually includes the same drugs, although with different doses, and administration times and methods, but there is no indication of decisive beneficial changes.

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a neoplasia of lymphocyte precursor cells (lymphoblasts) which originates in the bone marrow, invades other organs, and can progressively substitute normal hematopoietic cells. Lymphoblasts can be of the B or T cell lineage. In the case of NK cells, since they show functional and immunophenotypic similarities to T cells, they are included within this group (WHO, 2008). There have been unquestionable advances in the knowledge about the cytogenetic and molecular alterations that explain the participation of certain mutations in the generation of leukemic cells as a mechanism of action of several different etiological

***Corresponding author: Alvarado Ibarra Martha,**
Servicio de Hematología Centro Médico Nacional "20 de Noviembre". ISSSTE. Ciudad de México. México.

factors (Hsua *et al*., 2013; Wakeford *et al*., 2010; Kendall *et al*., 2011; Schuz, 2011). It is now possible to have a molecular classification of various subtypes of ALL in order to predict the evolution of the disease and the response to treatment (First, 1986; Arber *et al*., 2016; First, 1986). It is now considered possible to choose highly individualized treatments (Hunger *et al*., 2015). In patients under 15 years of age, even before these advances were known, there were frequent therapeutic successes in the form of prolonged remission and cures for childhood ALL. In the early 80's, an historic analysis (Holland, 1983), with strict methodology, showed that 25% of the children treated with chemotherapy (CTH) were still alive after 10 years. This cure rate has increased up to over 80%. Patients over 15 and under 40 years of age, termed the AYA group (adolescents and young adults) have benefited from the use of "pediatric-type" protocols, which include sequential, rotating, multiple chemotherapy (with different mechanisms of action), and short periods of rest. Indeed, when "adult-type" protocolswere used, disease-free survival (DFS) varied between 34-54% (Koharazawa *et al*., 2008; De Angelo, 2005). After the introduction of "pediatric-type" protocols, the situation changed in favor of greater efficacy without an uncontrollable increase in toxicity (Ram *et al*., 2012). In all the prospective and comparative programs (pediatric-type versus adult-type), the first shows a DFS to five years, of 61-78% (relative risk of 0.84 to 0.12 in favor of the pediatric programs) (Ram *et al*., 2012).

Conversely, and despite a greater knowledge of the disease, the outcomes for patients older than 40 are not good. In this group, most cases with ALL are generally too vulnerable to the toxicity caused by the "pediatric-type" programs. They usually tolerate less intensive protocols, but with a diminished efficacy in terms of DFS. That is, they are candidates to receive "adult-type" protocols which are currently rarely indicated for the AYA group. Additionally, although less frequently than in the elderly, at this age there can be comorbidities that can hinder antileukemic treatment. There are different treatment protocols for patients with Ph_{neg} ALL older than 40 (Fiere *et al*., 1993; Sebban *et al*., 1994; Ribera *et al*., 2005; Goldstone *et al*., 2008; Marks *et al*., 2009). In these studies, spanning from 1993 to 2009, the DFS to five years is 31-44% and the overall survival (OS) to five years, varies between 35 to 51%. As can be seen, in the last fifteen years the results have been comparable, without substantial progress. Furthermore, in these five studies, the age limits are from 15 to 48-64. This indicates that there were AYA patients included which, even though they were treated with "adult-type" programs, have a better prognosis than patients over 40, indicating that the survival data, strictly for patients over 40, are lower than reported. Hematopoietic stem cell transplantation (HPCT)is an available type of treatment. In general, allogeneic HPCT is considered to be more effective (Oliansky *et al*., 2012); its indication depends on the availability of a donor, the age of the patient, and the existence of comorbidities. At least for refractory Ph_{neg} ALL, this treatment can offer up to 36% OS at 2 years, without needing to discard, as a second option, autotransplantation (Pavlů *et al*., 2017). For patients in whom age is a limiting factor, reduced intensity transplants have been used. In a recent publication (Rosko *et al*., 2017) which studied patients between 55 and 72 years of age, where 71% were in remission and the remainder in second remission or refractory stage, reduced intensity HPCT was used, showing an OS of 38% to three years. The general results indicate a better outcome for groups of patients with ALL with a bad initial prognosis. The expression of different antigens that can be used as immunologic targets for the destruction of leukemic cells has allowed the development of monoclonal antibodies with antineoplastic efficacy, such as rituximab, inotuzumabozogamicin, and others (Jabbour *et al*., 2015; Buie *et al*., 2015). Blinatumomab is one of the most tested; in reality, it is not a monoclonal, it binds to CD19 and cytotoxic T-cells and promotes lysis by attracting perforins and granzymes (Wolach and Stone, 2015). It has been predominantly used for refractory or relapsed ALL and has shown efficacy for eliminating minimal residual disease by molecular mechanisms, thus obtaining complete remission (Wolach and Stone, 2015) and generating optimism for its eventual use for ALL in older patients. The purpose of this study is to disseminate our results after using a local protocol (LAL10), intensive and with curative purposes, in patients with Ph_{neg} ALL who are over 40 years of age but are in condition to receive intense chemotherapy, who were treated in our Service between 2001 and 2015.

PATIENTS AND METHODS

From 2001 up to 2015 an intensive chemotherapy program with curative purposes was implemented, named LAL10. It was directed toward patients older than 40 years of age with a diagnosis of *de novo* ALL, in conditions to receive treatment, and with no upper age limit. Patients were evaluated after the application of the first chemotherapeutic dose. Patients with leukemia with previous use of antineoplastic agents or with Ph+, were excluded. Additionally, patients who abandoned treatment or were then treated with HPCT were eliminated from the group. The following variables were studied: Age, sex, time course of the disease, initial clinical data, visceromegaly and adenopathies; extramyeloid infiltration; initial blood counts, initial bone marrow, blood chemistry profile, initial lactate dehydrogenase, and karyotype. Hyperglycemia was considered above 150 mg/dL determined during the first week of induction and persistent (or dependent on the use of hypoglycemic drugs). Patients were classified according to FAB and immunophenotype. All were included in the LAL10 therapeutic program. The quantity of blasts in bone marrow was registered on day 14 of induction therapy and on day 28, to determine whether remission was achieved. The times of chemotherapy administration were measured and compared to the established program. It was considered delayed if the time of application was greater than 20%more that that established in the program. The principal events considered were failure, relapse (time and place) and death (time and cause). We searched for prognostic factors in terms of relapse-free survival. For patients in continuous complete remission, follow-up was ceased at five years (60 months) after initial remission.

Definitions

Disease-free survival (DFS): Time that the patient remains alive after having reached complete remission and without having a relapse.

Event-free survival (EFS): Time that the patient remains alive from the beginning of induction chemotherapy administration without an event defined as failure, demise or relapse.

Overall survival (OS): Total follow-up time during which the patient remains alive, from his inclusion in the study until his demise.

Complete remission (CR): Disappearance of all clinical manifestations attributed to the disease. Normalization of the complete blood count. Bone marrow with normal hematopoiesis and less than 5% blasts.

Delay: Time greater than that programmed (greater than 20%) in relation to the calendar defined for the administration of chemotherapies.

Events

Failure: More than 5% blasts in the bone marrow, after finishing induction therapy.

Demise: Death occurring after initiating induction chemotherapy until the end of the follow-up.

Relapse: Data showing leukemic activity in bone marrow aspirate, CNS or other extra myeloid site, after having reached complete remission.

Myeloid relapse: More that 5% blasts in the bone marrow with alterations in the proportion of normal cells, after having reached complete remission.

CNS relapse: Blasts in cerebrospinal fluid after reaching complete disease remission.

Extra myeloid relapse: Infiltration to other organs, different from the central nervous system, as demonstrated by histopathology.

Elimination: Suspending follow-up of a patient due to treatment abandonment

LAL10 protocol (Table 1).

Statistical Analysis

SPSS version 20.0 for windows was used. The descriptive analysis was carried out with measures of central tendency and dispersion, absolute measures and percentages of the variable type. The prognostic data search was carried out using ANOVA, Chi^2 and Kruskal-Wallis. For overall survival and relapse-free survival, we used Kaplan Meier. Statistical significance was considered at $p<0.05$. Confidence interval was 95%.

RESULTS

One hundred and fifty-three new ALL cases (age greater than 40) were treated, 36 of which were over 65 years old. In this study, only 84 patients were included who were in conditions to receive intensive chemotherapy? The median was 48 years old; 26 patients were over 50 (31%). There is a predominance of females. The basic initial data is included in Table 2. Splenomegaly was found in 22 patients; hepatomegaly in 24 patients and adenopathies in 19. The dimensions are found in Table 2. Over half of the patients had some type of comorbidity. The most frequent was hyperglycemia in 44 cases (52%) of which 10 were previously known diabetics. Other comorbidities were arterial hypertension in 2 and others, including two Down syndrome patients. The most elevated level of leukocytes was 553 x 10^9/L. Forty patients had an amount greater to 25 x 10^9/L. In bone marrow, the lymphoblast counts ranged from 40 to 100% with a median of 84%. The cytomorphological types (L1/L2) were 30/54. The immunophenotypic results were: 8 Pro B, 70 Pre B, 5 mature and 1 T. The cytogenetic study showed a complex karyotype and two trisomy 21 patients. The fate of the patients is presented in Table 3.

Table 1. Chemotherapy program LAL10. 1.0 Induction. 2.0 Intensification. 3.1 to 3.3 Consolidation. 4.0Prophylaxis CNS; 5.0 Maintenance; 6.0Periodic reinduction. During Consolidation, each cycle is repeated 3 times. After 4.0, the sequence is 5.0, 6.0, 3.1,3.2, 3.3, 5.0… until completing 3 years in continuous remission. Between each cycle, there are 14 days of rest

Phase	Drugs	Dose	Admin	Days
1.0	Dexamethasone	15 mg/m2	IT	-4 to -1
	Methotrexate	12.5 mg	IT	0
	Cytarabine	50 mg	IT	0
	Dexamethasone	4 mg	IT	0
	Daunorubicin	60 mg/m2	IV	0 and 1
	Cyclophosphamide	750 mg/m2	IV	2
	Vincristine	2 mg	IV	1, 8, 15, 22
	Prednisone	100 mg/m2	OA	1-7 and 15-22
	Asparaginase	6000 u/m2	IM	8, 15, 21,28
2.0	Cytarabine	2 g/m2 bid	IV	1 to 4
3.1	Dexamethasone	4 mg	IT	1
	Methotrexate	12.5 mg	IT	1
	Vincristine	2 mg	IV	1
	Methotrexate	1 g/m2	IV	1
3.2	Cyclophosphamide	750 mg/m2	IV	1
	Daunorubicin	50 mg/m2	IV	1
	Vincristine	2 mg	IV	1
	Prednisone	100 mg/m2	OA	1 to 5
	Asparaginase	6000 u/m2	IM	5
3.3	Etoposide	150 mg/m2	IV	1 to 3
	Cytarabine	300 mg/m2	IV	1 to 3
	Asparaginase	6000 u/m2	IM	4
4.0	Methotrexate	12.5 mg	IT	1, 4, 8, 12
	Dexamethasone	4 mg	IT	1, 4, 8, 12
5.0	Mercaptopurine	100 mg/m2	OA	1 to 28
	Methotrexate	12.5 mg	OA	1 to 28, 2X week
6.0	Methotrexate	12.5 mg	IT	1
	Dexamethasone	4 mg	IT	1
	Cyclophosphamide	600 mg/m2	IV	1
	Cytarabine	100 mg/m2	IV	1 to 4

Granulocyte Colony Stimulating Factor in 1.0 and 2.0

The frequency of CR was 74 (88%) and 10 patients were refractory. The most frequent event was relapse in 47.6% of cases: 35 were in bone marrow, 3 in skin, and 2 in central nervous system. Among those eliminated, three passed on to allogeneic HPCT. Follow-up for patients with DFS is shown in Figure 1. The probability of DFS to five years is 0.21 with a median of 14 months. The probability of EFS (Figure 2) to five years is 0.17 with a median of 10 months. There were 32 deaths, of which 20 followed failure or relapse. The remaining 12 occurred between induction and up to the ninth month; the mode is 1 month. There were 7 deaths during induction. Causes of death were infection (24) and hemorrhage (8). The probability of OS to five years was 0.39 with a median of 25 months. In the analysis of all of the basal data, the majority did not show association with DFS (p>0.07). There was association when the initial leukocyte count was greater than 25 x 10^9/L with a median DFS of 10 months. When the count was less than this, the median was 18 months (p=0.03). Cytomorphology showed L1 and L2 with medians of 21 and 13 months (p=0.05). The absence and presence of hyperglycemia showed medians of 23 and 10 months (p=0.006).

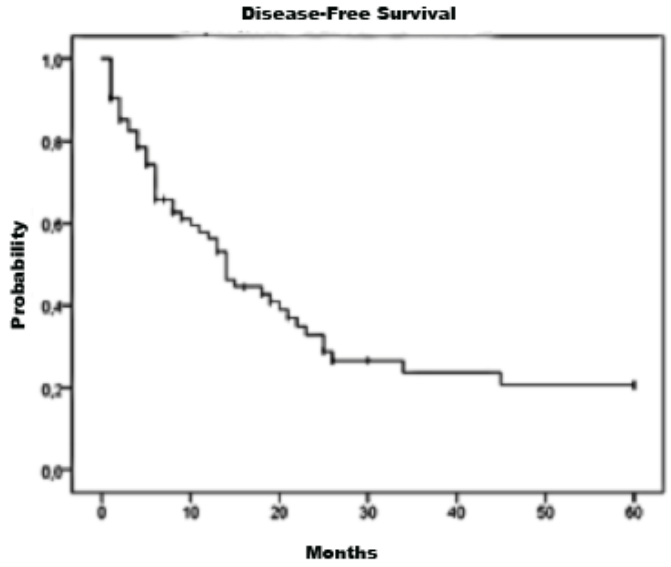

Figure 1. Disease-Free Survival (DSF) to 5 years = 0.21. Median = 14 months

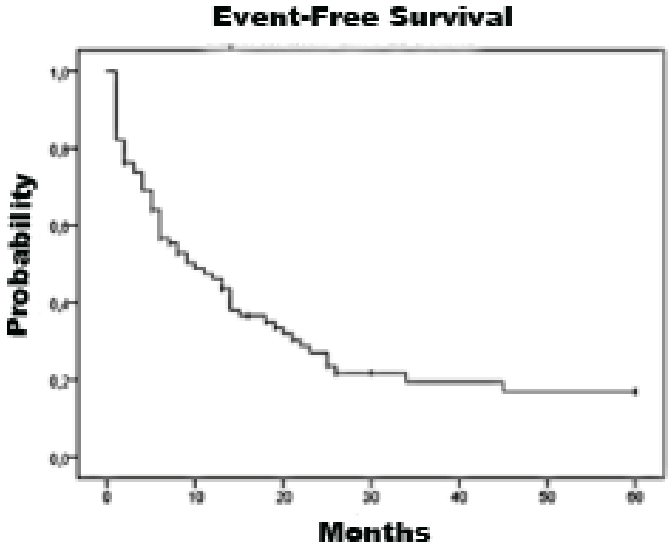

Figure 2. Event-Free Survival (EFS) to five years = 0.17. Median = 10 months

This indicator was significantly associated with a delay in compliance with the program (p=0.0001) and a greater frequency in the number of deaths by infection (p=0.03).

DISCUSSION

It´s well known that there is a greater incidence of ALL in children younger than 15, with a subsequent reduction until reaching 60 years of age, where there is another increase. However, the amount of publications is greater for the population of children, then for the AYA group and less frequently for the older population. Even in these studies with older patients, it is frequent to find patients of 15 or more years of age considered as adults (Fiere *et al*., 1993; Sebban *et al*., 1994; Ribera *et al*., 2005).

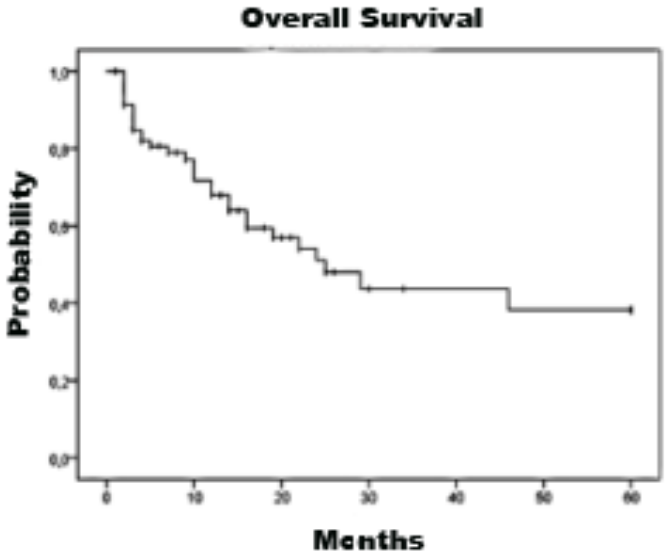

Figure 3. Overall Survival (OS) to five years = 0.39. Median = 25 months

Thus, the therapeutic results show an inevitable bias resulting from the inclusion of younger patients. In our population, we only included patients which are not part of the group of adolescents and young adults and who did not receive "pediatric type" therapeutic programs. The upper age limit of our population, no patients older than 73, stems from the initial clinical state, which did not permit the use of the protocol used herein. Of all of the patients who were admitted to our Service and were over 40, only a little more than half, were able to receive the treatment. This sample has a predominantly female population; it is generally considered that there is a greater frequency in males, although a number of regional variations are accepted (Sive *et al*., 2012; Redaelli *et al*., 2005). In general, ALL in older adults initially shows slower evolution than in the AYA group (Gökbuget, 2013). In our experience, this observation is real; our data shows a median evolution of 7 weeks while a recently published report showed a median evolution of 4 weeks in the AYA group with (p=0.0001)[28]. However, when the disease is established, the magnitude of tumoral load seems comparable. The main comorbidity found was hyperglycemia at the initiation of the treatment, with or without a history of it, in half of the patients. In Mexico, the general incidence of diabetes is 9.2%, although it is estimated that this number is inferior to reality[29]. In any case, in our patients, the elevated presentation of hyperglycemia is related with the high doses of dexamethasone and prednisone, as

described in other studies. A recent Mexican study (Gonzalez-Gonzalez *et al*., 2013), in patients with ALL and treatment with corticosteroids, the incidence of hyperglycemia was 68.7%. Another study carried out in the United States[31], shows a frequency of 37%.

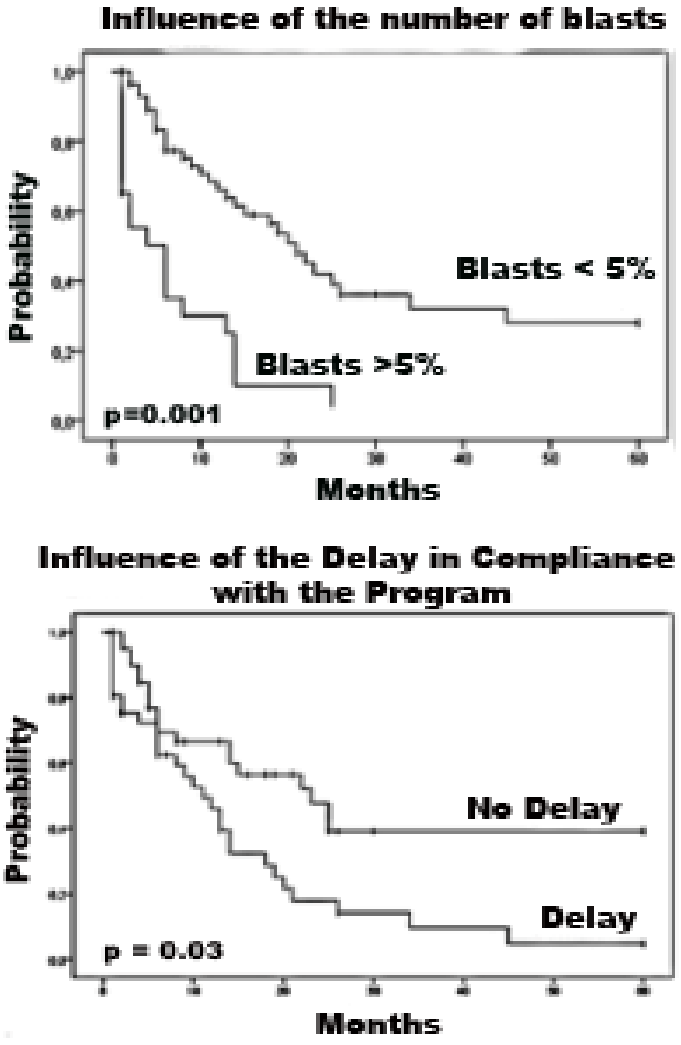

Figure 4. Disease-Free Survival (DFS). Prognostic influence of the blast count on day 14 of Induction and of the delay in compliance with the chemotherapy program

Although the dose and delivery no doubt influence these frequencies, it can be concluded that that hyperglycemia is a very frequent complication. The negative impact of hyperglycemia on DSF and its relationship to greater frequency of infections as cause of death is noteworthy. These results are not a new finding. At least since 2004, there have been reports about this consequence when using the Hyper-CVAD therapeutic program (). This well-known scheme is not very different from the one used herein, in terms of the high doses of glucocorticoids. In our study, hyperglycemia is also associated with lower DSF, but does not behave like an independent factor and is associated with a delay in punctual compliance of the chemotherapeutic program. There are, in effect, frequent delays in the application of the drugs because of infectious complications, more severe and lethal in patients with hyperglycemia. The initial numbers of leukocytes were generally found to be elevated, based on the measure of central tendency, and the leukocytosis greater than 25 x 10^9/L was found to be a negative prognostic factor. This observation has been confirmed in various publications, having similar cutoff numbers orup to 30 x 10^9/L. Among the different data, before chemotherapy, the ones considered to be most relevant as diagnostic factors are age and leukocyte numbers (Bassan and Hoelzer, 2011). The negative influence of L2 cytomorphology, found in our study, is referred to in publications of the last century (Chessells, 1982), although the assessment that this variety is more aggressive than L1, was not unanimous. In reality, the existence of other factors, more objective, sensitive and specific have distanced the FAB classification from prognostic transcendence.

Table 2. Basal Data

Variable	Result
Sex (f/m)	47/37
Age (median/limits)	48/41-73
Previous evolution (weeks)	7/1-16
Splenomegaly (cm) (media/limits)	4/2-12
Hepatomegaly (cm) (media/limits)	4/2-20
Adenomegalies (cm) (media/limits)	2/1-4
Hematocrit % (media/limits)	25/7-39
Leukocytes x 10^9/L (media/limits)	55.4/0.4-553
Blasts in blood (media/limits)	38/0-191
Platelets x 10^9/L (media/limits)	81/4-437
Lactic dehydrogenase IU/L (media/limits)	623/112-3,873
Comorbidities (yes/no)	49/35
Hyperglycemia (n/%)	44/52

Table 3. General therapeutic results. Complete remission post induction = 74 (88.1%). Death during induction = 7 (8.3%)

Event	N=	%
Relapse	40	47.6
Failure	10	11.9
Death	12	14.3
Abandonment	8	9.5
Without event	14	16.7
Total	84	100

After antileukemic treatment was initiated, we found other data that demonstrated predictive value. The blast count on day 14 of induction, above 5%, was related to greater relapse and with chemotherapy-resistant disease. Currently, this indicator is no longer used and is advantageously substituted by the determination of minimal residual disease (Spinelli *et al*., 2014), which allows for better therapeutic decision making, even after induction of remission. Nevertheless, the prediction of therapeutic failure using blast count on day 14 is effective, in our experience. Additionally, the delay in compliance of the chemotherapeutic program also has negative prognostic influence; a lag in the delivery of the cycles results in a longer rest period for the neoplastic cells and favors their proliferative activity. The induction phase of the LAL10 program was satisfactory. Mortality is low compared to other studies (Sive *et al*., 2012; Ribera *et al*., 2016) that show over 13%. Its efficacy, measured as the frequency of CR, is between the limits of other recognized programs (74 to 90%). These results are affected by the age of the population studied, since the greatest amount of remissions are related to the inclusion of young patients, often mixed in with patients older than 40 (Bassan and Hoelzer, 2011; Ribera *et al*., 2016). There is a consensus that post induction treatment is necessary, even in older patients that receive intensive treatments. In one study (with Hyper-CVAD) a significant difference (p=0.001) in DSF was found in favor of those who received maintenance (Landsburg *et al*., 2013). We have not studied the efficacy of the LAL10 program without maintenance, however, even with maintenance; the DSF reported herein indicates its poor

efficacy. In our experience, relapse constituted the most frequent event, although it is not radically different from that observed in other studies with Ph_{neg} patients of comparable ages. If these are in a range of 50 to 65-70 years, the OS results to 5 years are 23 to 30% (Sive *et al*., 2012; Sancho *et al*., 2007; Pullarkat *et al*., 2008). An epidemiological review[42] found that in patients 60 to 70 years old, the OS to five years was 20.4% in the period between 2002-2011. It is evident that the results with chemotherapy cannot be considered satisfactory, particularly when compared to the AYA or younger than 15 groups. Among the different protocols, the chemotherapy generally includes the same drugs, although in different doses, and administration times and methods; however, the results don't indicate decisive beneficial changes. Immunotherapy promises to improve the results. Blinatumomab, one of the most tested, has demonstrated efficacy in neutralizing MRD, after chemotherapy has failed to do so (Buie *et al*., 2015). Recently, the results of a comparative study were published, Blinatumomab versus an historic control. Patients were 189 and 694 (up to 1112 with OS data), older than 18 (58% over 35 years of age) and with refractory or relapsed ALL. The CR was 43 and 24%; the OS was 39 and 17% to 12 months (Gökbuget *et al*., 2016). Lately, new information has come forth: a multicentric, randomized and prospective study using Blinatumomab (271 patients) and chemotherapy (134 patients) for patients with refractory or relapsed ALL found a CR of 44 and 25% (p=0.001); the OS was 7.7 months and 4.0 months (p=0.01) (Kantarjian *et al*., 2017). The superiority of Blinatumomab must be tested in coming years and much can be speculated about its final role for the treatment of ALL, but there are positive expectations for the treatment of patients older than 40.

Conclusion

In our experience, relapse was the most common event. Although this is not radically different from the observations in other reports found in the literature with Ph_{neg} patients, these results cannot be satisfactory, particularly when compared to the AYA or the under 15 groups. In the different protocols that have been carried out around the world, chemotherapy generally includes the same drugs, although with different doses, and administration times and methods, but do not indicate decisive beneficial changes.

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