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ORIGINAL ARTICLE

Hypersensitivity reactions associated with the use of asparaginase in children with acute lymphoblastic leukemia

Reacciones de hipersensibilidad asociadas al uso de asparaginasa en niños con leucemia linfoblástica aguda

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What do we know about the subject matter of this study?

We know that pediatric patients with acute lymphoblastic leukemia may present hypersensitivity reactions to asparaginase, to different degrees and with possible effects on their prognosis.

What does this study contribute to what is already known?

This study provides local data on the incidence of hypersensitivity reactions to different formulations of asparaginase, indicating risk according to the protocol used, clinical manifestations, and survival. We propose a management algorithm, covering both immediate and future chemotherapy plans.

Abstract

The treatment of acute lymphoblastic leukemia (ALL) includes the use of asparaginase (ASP), a drug associated with hypersensitivity reactions (HSR) that requires discontinuing its use. **Objective:** To determine the incidence of HSR associated with ASP that require discontinuation of its use and describe them, and to verify if there is a relationship between HSR incidence and protocols or survival. **Patients and Method:** Retrospective study. Clinical records of all patients (1-15 years) diagnosed with ALL between January 2010 and December 2015 at the Hospital Luis Calvo Mackenna were reviewed. The incidence of HSR to ASP was determined and classified according to the CTCAE v5.0 severity score. We analyzed the relative risk of HSR using Fisher's test and the survival with the Kaplan-Meier estimator. **Results:** 110 patients were collected. During the first treatment (ALL-IC-BFM), the incidence of HSR to L-ASP was 55%, therefore it was changed to PEG-ASP as second-line treatment, and 44% of them had HSR, and ASP should discontinued in 25% of patients. Of all the HSR to ASP, 77% were anaphylactic (CTCAE 3-5). Patients treated with augmented IB protocol were

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at higher risk of not completing ASP treatment due to HSR, RR 3.81 (95% CI, 1.98-7.31, p = 0.0001). Patients without HSR in ALL-IC-BFM were at lower risk of relapse, HR 0.29 (95% CI, 0.14-0.62, p = 0.0013). Considering all treatments (ALL-IC-BFM and relapse), patients who completed the ASP treatment had higher overall survival, HR 0.20 (95% CI, 0.07-0.57, p = 0.0026). **Conclusions:** HSR to ASP that require discontinuation of treatment are frequent in children with ALL, most of them were severe anaphylactic reactions. This study suggests a better prognosis in patients without HSR to ASP.

Introduction

Acute lymphoblastic leukemia (ALL) is the most frequent malignant disease in children and accounts for 25% of childhood cancers[1]. In Chile, the annual rate is 39 per million children aged under 15 years[2]. Pharmacological ALL treatment involves the use of asparaginase (ASP), an enzyme of bacterial origin capable of degrading L-asparagine into ammonium and aspartate, which leads to depletion of the extracellular pool of this amino acid. Lymphoblasts lack ASP and must absorb the L-asparagine required for their metabolism from the extracellular pool. When it is not available, the metabolism of leukemia cells is inhibited, inducing apoptosis[3]. It has been proven that with ASP activity values > 0.1 IU/ml in serum, it is possible to achieve the desired therapeutic effect[3,4].

There are currently three forms of ASP, two of which are *Escherichia coli*-derived (native [L-ASP], and pegylated [PEG-ASP]) and one derived from *Erwinia chrysanthemi* (*Erwinia*-ASP). These three drugs present differences in dosage, activity, half-life, commercial value, immunogenic profile, and risk of side effects, such as thrombosis, hyperglycemia, pancreatitis, hepatotoxicity, among others[3-5].

Since they are of bacterial origin, they can also generate hypersensitivity reactions (HSR) in 13-42% of patients[3,6-9]. These HSR are usually mediated by neutralizing antibodies that inactivate ASP, reducing its antileukemic effect. Likewise, up to 30% of patients may present "subclinical hypersensitivity", also known as "silent inactivation", where antibodies are present despite the absence of clinical signs[4,10].

Finally, the increase of serum ammonium due to the enzymatic activity of ASP can have a very variable clinical expression, from asymptomatic to severe neurological symptoms[11,12]. Another manifestation to consider is the "allergic-type reaction", where appear symptoms that seem to be hypersensitivity, but without the presence of antibodies or a decrease in ASP activity.

All patients at the *Hospital Dr. Luis Calvo Mackenna* (HLCM) with ALL without Philadelphia chromosome (Phi-), aged 1 to 15 years at diagnosis, are treated according to the ALL IC-BFM 2009 Protocol (Acute Lymphoblastic Leukemia Intercontinental Berlin-Frankfurt-Münster), where Chile is a member[13]. Both the protocol used in newly diagnosed ALL and relapsed ALL (Relapse Protocol 04.13)[14], include the use of ASP since several collaborative groups have demonstrated a higher response rate by including it in their schemes[1,4]. However, the adverse reactions associated with its administration make it necessary to change the formulations used and even to suspend its use definitively[9,15]. The prognosis of survival in children who have had to discontinue the use of ASP could be related to the total dose received.

The ALL-IC BFM 2009 includes L-ASP in the induction (IA) and re-induction (II) phases. A group of patients receives a randomized early intensification with another 12 doses of L-ASP (augmented IB) and those at high risk also receive it in consolidation (HR1-HR2-HR3)[13]. Patients presenting HSR change to PEG-ASP as second-line treatment. The relapse Protocol 04.13 includes PEG-ASP in each chemotherapy block[14].

The main objective of this study is to determine the incidence of HSR associated with the administration of ASP in children with ALL that require discontinuation of their use. The secondary objectives are to clinically describe the HSR associated with ASP, determine the incidence and type of HSR according to the formulation of ASP used, the percentage of patients requiring a change in the type of ASP or discontinuation of therapy, and the incidence of other complications associated with ASP; as well as verify whether there is an association between the presence of HSR and the protocol used, risk group, event-free survival (EFS), and overall survival (OS) of patients.

Patients and Method

Design

Retrospective cohort study, including all patients aged between 1 and 15 years with a diagnosis of B-cell or T-cell precursor ALL, diagnosed between January 2010 and December 2015, with treatment and follow-up until July 2017 at the HLCM. Children with translocation (9;22) or bilinear involvement were excluded.

Assessed data

The medical, nursing and pharmacy clinical records were reviewed. The following data were recorded: demographics (age, sex, concomitant pathologies), type of ALL (according to immunophenotype and risk group), ASP administration (formulation, dose, infusion time, total dose received, change to a second-line drug, reason for change, and causes of ASP discontinuation), HSR (clinical symptoms, severity of reaction according to the Common Terminology Criteria for Adverse Events (CTCAE) score version 5.0 (table 1), type of ASP causing the adverse reaction, protocol stage, time to occurrence, percentage of drug received, and treatment and response to it), discontinuation of ASP treatment due to other events (pancreatitis, hematopoietic stem-cell transplantation (HSCT), secondary malignancy or other reason), and the patient's current condition until the defined follow-up (in treatment with intensive or maintenance chemotherapy, follow-up, HSCT, or deceased)[16].

Ethical aspects

Patients over 18 years of age signed informed consent or the legal guardians if the patient was underage, and the informed ascent by those children aged between 12 and 17 years. The study was approved by the Pediatric Scientific Ethics Committee of the Eastern Metropolitan Health Service.

Statistical Analysis

Incidence, mean, and median tests were used as well as the Fisher's test for categorical variables and T-Student for the quantitative comparisons. Event-free and overall survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. The data were analyzed with the GraphPad Prism 5.0 software. A p-value < 0.05 was considered statistically significant.

Table 1. HSR to Asparaginase severity assessment (CTCAE 5.0 adaptation)

Grade of HSR	Description
Grade 1	Rash or transient erythema, low-grade fever < 38°C.
Grade 2	Rash or erythema, abdominal pain, pharyngeal itching, cough. It then responds quickly to symptoms' treatment.
Grade 3	Anaphylaxis. Symptomatic bronchospasm, with or without urticaria; edema / angioedema.
Grade 4	Life threatening anaphylaxis, hypotension; requires immediate intervention.
Grade 5	Death

HSR: hypersensitivity reaction

Results

Patients

Between January 2010 and December 2015, 118 patients aged from 1 to 15 years with Ph-negative ALL were diagnosed at HLCM. Of these, 110 received the intensive phase of treatment at this center. Table 2 shows patients' demographic data.

Incidence of HSR

Of the 110 patients included, in the first treatment (ALL-IC BFM 2009), 61 presented HSR to L-ASP, with 55% of incidence. All of them continued therapy with PEG-ASP as second-line treatment and 27 children (44%) presented an HSR. Therefore, 25% of the patients failed to complete this protocol due to HSR to both formulations.

Regarding the 32 patients who relapsed and were treated with Protocol 04.13 including PEG-ASP in first-line therapy, 11 (34%) had to discontinue the drug due to HSR during this treatment. Of the remaining 21 relapsed children, 10 could not receive PEG-ASP due to history of HSR during the first ALL treatment. Therefore, 66% of relapsed patients failed to complete the protocol due to HSR before or during this treatment.

Clinical Presentation

One hundred and one cases of HSR to one of the ASP formulations were identified, of which 4 could not be described and classified due to lack of information. In most of the remaining 97 cases, the HSR occurred 15-20 min after starting the infusion, where 30-40% of the programmed dose was administered. 77% of the HSR were anaphylactic reactions, classified as CTCAE grade 3-5. One patient died of cardiac arrest associated with the use of PEG-ASP. Table 3 shows the data of L-ASP and PEG-ASP administration in patients with HSR.

Regarding the signs and symptoms according to ASP formulation (table 4), the most frequent were cutaneous and respiratory manifestations, angioedema, and abdominal pain. When comparing both groups, the only symptom/clinical sign observed in which there was a statistically significant difference was dyspnea and decreased oxygen saturation ($p = 0.03$). In relation to this variable, not only was the percentage of patients in the group with a reaction to PEG-ASP higher, but they also tended to show greater obstructive bronchial signs and require greater oxygen intake.

The history of previous L-ASP reactions did not determine differences in the severity of HSR to PEG-

Table 2. Demographic characteristics of children with ALL

	Patients with ALL (total cohort) (n = 110)	Patients with reaction to L-ASP and/or PEG-ASP (n = 76)	Patients without reaction to L-ASP and/or PEG-ASP (n = 34)
Age			
- Median (years)	5	5	5
- Range (years)	(1 - 15)	(1 - 15)	(1 - 14)
Sex			
- Male	54	38	16
- Female	56	38	18
ALL immunophenotype			
- B cell lineage	106	74	32
- T cell lineage	4	2	2
Risk group			
- Standard	22	11	11
- Intermediate	72	52	20
- High	16	13	3
Relapses			
- Late	12	11	1
- Early	11	11	0
- Very early	9	8	1
CNS Status			
- Status 1	82	56	26
- Status 2	25	17	8
- Status 3	3	3	0
IB augmented received			
- Yes	29	25	4
- No	81	51	30[1]
Current condition, n (%)			
- Maintenance (CR1)	8 (7)	4 (5)	4 (12)
- Follow-up	68 (62)	43 (56)	25 (73)
- HSCT	6 (5,5)	5 (7)	1 (3)
- Treatment discontinuation	1 (1)	1 (1)	0 (0)
- Relapse protocol (CR2)	6 (5,5)	5 (7)	1 (3)
- Palliative care	2 (2)	2 (3)	0 (0)
- Dead	19 (17)	16 (21)[2]	3 (9)[3]

ALL: acute lymphoblastic leukemia, L-ASP: L-asparaginase, PEG-ASP: Pegylated-Asparaginase. CNS: central nervous system, CR1: first complete remission, CR2: second complete remission. HSCT: hematopoietic stem cell transplantation. [1]One patient died under Protocol IA. [2]Fourteen patients died because of relapse, one due to varicella (during follow-up), and one due to cardiorespiratory arrest associated with the administration of PEG-ASP. [3]Two patients died during their first treatment due to infectious complications and one patient, due to relapse.

ASP. Moreover, the patient who died and one of the children with more severe bronchial obstruction did not have HSR to L-ASP and the reason for the change was the start of the relapse protocol.

Other complications

Other complications associated with the use of L-ASP were: pancreatitis (n = 4), hyperglycemia (n = 2), and thrombosis (n = 4; 2 of them in the venous sinuses of the CNS). In relation to PEG-ASP, pancreatitis (n = 3), thrombosis (n = 1), and hematoma (n = 1) were observed. All patients with pancreatitis discontinued the use of ASP and due to this cause, and 2 of them could not receive PEG-ASP in the Relapse Protocol.

Relationship with protocol and risk group

The highest number of HSR to L-ASP occurred in the first dose of Protocol II, representing 32% of cases, followed by 27% of augmented IB Protocol. The highest frequencies of HSR to PEG-ASP occurred in augmented Protocol IB (27%), Protocol II (22%), and F2 relapse (19%).

The 11 patients with a reaction during the first administration of PEG-ASP had history of hypersensitivity to L-ASP and in 8 of them, the interval between the two drugs was greater than 14 days (median 2 months).

When comparing the incidence of HSR in patients exposed to augmented Protocol IB (25/29) versus

Table 3. Administration data of L-ASP and PEG-ASP to patients with HSR

	Patients with reaction to L-ASP (n = 63)	Patients with reaction to PEG-ASP (n = 38)
N° of HSR, according to protocol (%)		
- ALL-IC BFM 2009 (n = 110)	61 (56)	27 (44)[2]
- Relapse protocol 04.13 (n = 32)	2 (6)[1]	11 (34)[3]
N° of previous doses		
- Median [range]	8 [0 - 25]	1 [0 - 4]
Time between beginning of infusion and reaction (minutes):		
- Median [range]	20 [5 - 150[4]]	15 [5 - 170[4]]
Treatment used during reaction:		
- Infusion interruption or no treatment	2	0
- First-line treatment 5	47	32
- Second-line treatment 6	10	6
- Epinephrine	1	1
- Advanced CPR	0	1
Response to treatment		
- Symptoms' remission	54	32
- Required second-line treatment	3	2
- Required hospitalization or prolonged observation	3[7]	2
- Death	0	1
Reaction severity, n (%)		
- Grade 1	2 (3)	0 (0)
- Grade 2	11 (18)	9 (24)
- Grade 3	46 (77)	24 (65)
- Grade 4	1 (2)	3 (8)
- Grade 5	0 (0)	1 (3)

L-ASP: L-asparaginase, PEG-ASP: Pegylated-Asparaginase, HSR: Hypersensitivity reaction. CPR: cardiopulmonary resuscitation. [1]Before 2013, some patients received L-ASP in the relapse protocol. [2]The percentage was calculated among only the children that received PEG-ASP. [3]Considering the cases among only the patients that were able to receive PEG-ASP (n=20), the percentage increases to 55%. [4]In both groups, the time of drug administration lasted more than usual in one patient. [5]Hydrocortisone, oxygen, chlorphenamine. [6]Methylprednisolone, bronchodilators, analgesia, ranitidine. [7]One patient that was hospitalized because of 40°C fever (had also dyspnea, tachycardia, chills) had history of one-week respiratory symptoms.

Table 4. L-ASP- y PEG-ASP-associated HSR symptoms

	Reaction to L-ASP (n = 60) n (%)	Reaction to PEG-ASP (n = 37) n (%)	P value
Erythema - rash - urticaria	38 (63)	30 (81)	0.07
Facial edema - angioedema	23 (38)	17 (46)	0.66
Abdominal pain	21 (35)	13 (35)	> 0.99
Dyspnea - desaturation	20 (33)	21 (57)	0.03
Cough	19 (32)	2 (16)	0.10
Nausea - vomiting	15 (25)	12 (32)	0.49
Itch	10 (17)	9 (24)	0.43
Tachycardia	7 (12)	4 (11)	> 0.99
Fever - chills	6 (10)	0 (0)	-
Cervical, precordial, or lumbar pain	6 (10)	0 (0)	-
Agitation - Irritability	3 (5)	3 (8)	0.67
Headache	3 (5)	0 (0)	-
Paresthesia - dizziness	3 (5)	0 (0)	-
Hypotension	2 (3)	1 (3)	> 0.99
Asystole	0 (0)	1 (3)	> 0.99
Other[1]	4 (1.7)	1 (3)	-

HSR: hypersensitivity reaction, L-ASP: L-Asparaginase, PEG-ASP: Pegylated-Asparaginase. [2]Other: red eye-epiphora (1), sweating (1), hypertension (1), sphincter relaxation (1).

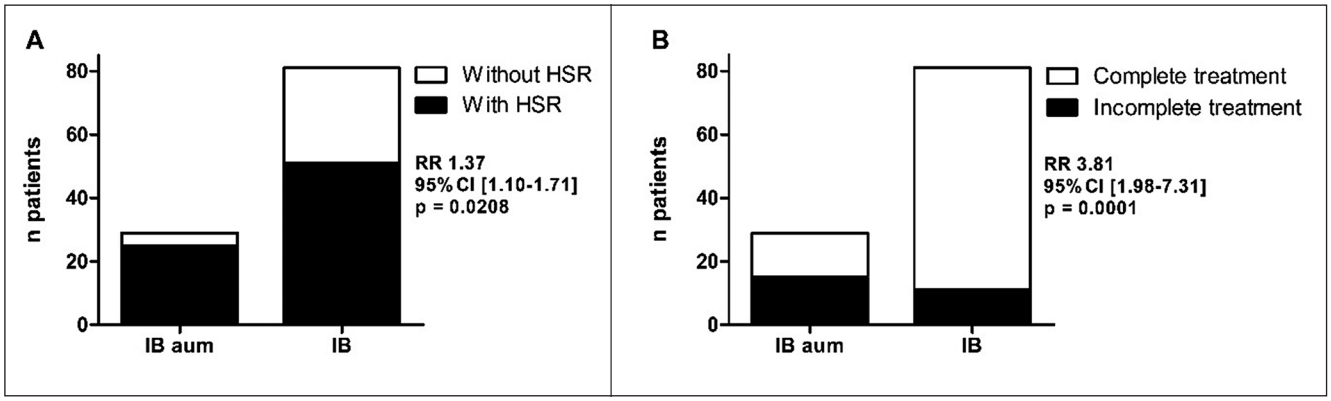

Figure 1. Comparison of patients who entered the IB protocol versus augmented IB protocol and the risk of presenting HSR (A) and the risk of failing to complete treatment with any formulation of ASP (B). RR: relative risk, IB aum: augmented IB, HSR: hypersensitivity reaction. Fisher exact test.

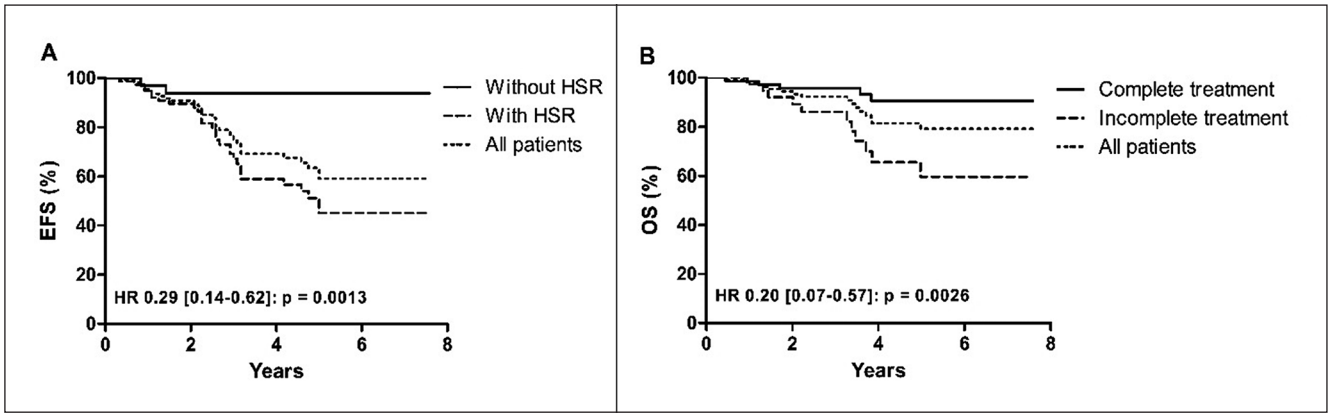

Figure 2. Comparison of EFS between patients who present HSR versus those who do not present HSR (A). Comparison of OS between patients who complete treatment with ASP versus those who do not complete treatment with ASP (B). HR: hazard ratio, EFS: event free survival, OS: overall survival, ASP: asparaginase, HSR: hypersensitivity reaction. Log rank test.

those exposed to Protocol IB (51/81), we observed a relative risk (RR) of HSR of 1.37 (95% CI, 1.10-1.71, p = 0.0208), while the RR of failing to complete treatment with ASP if the patient is treated with augmented Protocol IB compared with Protocol IB is 3.81 (95% CI, 1.98-7.31, p = 0.0001) (figure 1).

Considering the ALL risk group, there were no statistically significant differences between the standard, intermediate, or high risk and occurrence of HSR.

Relationship with EFS and OS

When analyzing survival, we found that patients without HSR were at 71% lower risk of relapse than those with HSR during the first treatment, HR 0.29 (95% CI, 0.14-0.62, p = 0.0013), with no difference in OS (figure 2).

In patients who underwent the first treatment with ALL-IC BFM protocol, we found a trend of higher EFS in patients who completed ASP treatment than those who did not; however, this difference was not statistically significant (p = 0.0714). On the other hand, when analyzing OS between these groups, including first and relapse treatment, we found that patients who completed ASP treatment had a higher OS than those who did not, HR 0.20 (95% CI, 0.07-0.57, p = 0.0026) (figure 2).

There were no differences in EFS or OS between patients who received more than 50% of the total dose of ASP and those who received less than 50%.

Discussion

The percentage of children who had to discontinue ASP treatment due to HSR to both formulations during the newly diagnosed ALL protocol was 25% and increases to 38% when considering the overall treatment, including relapses. The incidence of HSR to

L-ASP and PEG-ASP observed in our study is within that reported in Chile (40%) and other groups (10-40% approximately)[8-10,17-23].

Several factors could explain the large width of the range. On the one hand, studies by the St. Jude Children's Research Hospital (SJCRH) and the Children's Oncology Group (COG) have found genetic polymorphisms associated with a higher probability of hypersensitivity to ASP within the Caucasian, Latino, or other populations[18,24-26]. On the other hand, it is not fully clarified whether the intravenous (IV) route of administration, which has the advantage over the intramuscular (IM) route in avoiding the pain and anxiety that this produces in children, favors the appearance of HSR. Hasan H. et al performed a meta-analysis (n = 752) that showed a 23.5% of risk of presenting hypersensitivity when using the IV route (95% CI: 14.7-33.7) and 8.7% using the IM route (95% CI: 5.4-12.8), with an adjusted OR of 2.49 (95% CI: 1.62-3.83)[27]. In Chile and other countries, the ASP administration protocols use the IV route, thus a strategy to reduce cases of HSR could be to change to the IM route, using local anesthesia methods, since ASP injection is particularly painful.

The incidence of our study is established according to the information and diagnostic elements available in Chile, excluding the possible cases of silent reactions and allergic-type reactions, due to the absence of implementation of these methods in the country. This is important when making decisions to change or suspend this line of treatment, considering that patients could be classified as allergic to ASP, without presenting HSR that require this management, or that we could maintain the treatment with an ASP formulation that is not being effective.

The relationship between antibody concentration and ASP activity has not always been observed, so it would be extremely important to establish the evaluation of ASP activity, which has been analyzed in several studies[28-32]. In Europe, the Dutch Childhood Oncology Group, the Italian Association of Pediatric Hematology and Oncology (AIEOP), the BFM, and others recommend periodic measurement of ASP activity and anti-ASP antibody levels to adjust therapy according to the results since there is evidence showing a higher 5-year EFS (90% vs 82%, $p < 0.04$) if the type of ASP is changed when silent inactivation is detected, despite that no statistically significant differences in OS have been observed[1,3,30,33]. Accordingly, although 100% of patients were classified by the Naranjo algorithm as "probable ADR", this percentage could change to "definite ADR" if the presence of antibodies and anti-ASP activity were detected[34].

In our group, there was a trend ($p > 0.05$) towards a higher EFS in patients receiving full ASP treatment in the ALL-IC BFM 2009 protocol, while if total follow-up is considered, including relapses, there was an OS with an 80% reduction in the risk of death in patients who completed all ASP treatment compared with those who did not, HR 0.20 ($p = 0.0026$) (figure 2). This indicates the benefit that can be obtained by maintaining this therapeutic line until the end of the intensive protocols. However, it should be considered that in the group of patients who complete treatment, there is a higher proportion of children with SR than in the group that does not complete treatment (26% vs. 8%, $p = 0.0242$), which could favor the tendency towards greater survival.

Expert recommendations propose the use of *Erwinia*-ASP, which would provide a third line of treatment in patients with HSR[33,35]. However, it has not yet been determined what the minimum dose of ASP is so that its discontinuation does not affect EFS and OS, which would define the need for this therapeutic alternative. Another factor to consider is that in Chile the cost of PEG-ASP is 5-7 times higher than that of L-ASP, therefore, a greater incidence of HSR to L-ASP that forces a change to PEG-ASP as a second line, leads to an increase in the total cost of treatment, emphasizing the importance of developing protocols with low incidence and efficient detection of HSR.

The number of reactions varied in the different phases of the protocols. It has been seen that the concentration of anti-ASP antibodies fluctuates throughout therapy, but since we did not have its measurement in our patients, we cannot know if there was a correlation between the incidence of reactions and the concentration of anti-ASP antibodies[29]. In our group, we observed a higher incidence of HSR (figure 1) in patients who received the augmented IB protocol ($p = 0.0208$), in addition to a higher risk of not completing treatment with ASP ($p = 0.0001$). This association is probably due to the higher dose and frequency of ASP that these children are exposed to compared with those in protocol IB, which could have favored their sensitization, making it less feasible to complete the treatment, regardless of the ASP formulation. This suggests the relevance of developing protocols that decrease the risk of HSR in order to not discontinue this therapy early.

Within the total number of reactions, we observed a high percentage of anaphylaxis grade 3 and 4 according to CTCAE 5 in our group for L-ASP 77% and 2%, and PEG-ASP 65% and 11%, respectively ($p = 0.0615$). Although we were unable to measure anti-ASP antibodies, we believe that they are real HSR since all patients included in these categories developed angioedema, dyspnea, oxygen desaturation, and/or bronchospasm. Browne E. et al found in 492 patients from the SJCRH 13% of HSR to PEG-ASP IV, of which 71% were gra-

de 3 according to the CTCAE, and only one patient with grade 4 HSR[21]. MacDonald T. et al observed in 128 children 14% of HSR to PEG-ASP IV used in first-line treatment, of which 28.6% were anaphylaxis[22]. A COG's study (n = 84) found 18% of anaphylaxis and another small study, 19%[9,23]. No deaths were reported in previous series. In our group, there was a tendency to clinically more severe HSR with the use of PEG-ASP, although with no statistically significant differences, except in dyspnea/desaturation.

There may be cases reported as grade 1-2 HRS that could be allergic reactions related to the infusion or to an increase in plasma ammonium, which can cause symptoms such as headache, nausea, vomiting, and lethargy[36,37]. The lack of ASP activity measurement could lead to false positives in the detection of HSR. In a small series, Kloos et al. found no statistically significant differences between the symptoms of antibody-mediated and other allergic reactions in a group of patients with grade 1-2 HRS according to the CTCAE[38].

Differentiating true HSR within our group would provide the chance to have fewer cases of ASP discontinuation and unnecessary switches to second-line therapy, considering that they accounted for 22% of the cases in our group of patients. A first approach could be to measure plasma ammonium in children with this type of HSR.

Most HSR were managed with antihistamines and

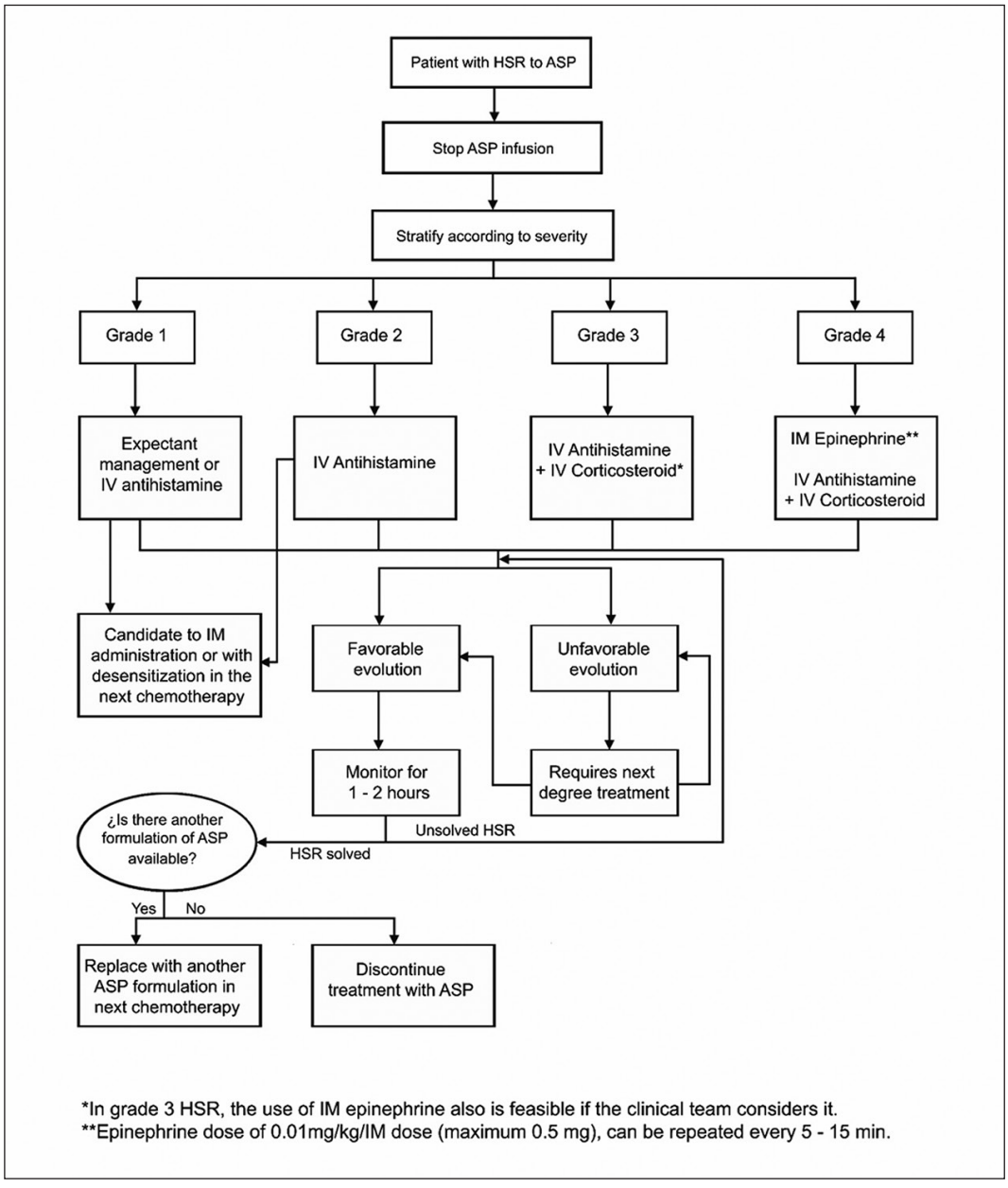

Figure 3. Management algorithm from hypersensitivity reaction to asparaginase according to modified CTCAE v5.0. HSR: hipersensitivity reaction, ASP: Asparaginase, IV: intravenous, IM: intramuscular

corticosteroids, adding oxygen administration in case of respiratory distress and desaturation. Although other groups also use these drugs in the management, clinical guidelines recommend the use of IM adrenaline as first-line therapy in anaphylactic reactions, which was the case in 77% of the children[9,39,40]. In our series, adrenaline was only used in 2 patients (table 3), with rapid clinical response. There were patients with prolonged HSR who could have decreased their symptomatology earlier with the use of IM adrenaline. Figure 3 shows our proposal of management algorithm according to the severity of HSR.

As reported in other studies, most of the HSR to ASP occurred during infusion, suggesting that they are IgE-mediated type 1 reactions, considering that IgM and IgG antibodies have also been detected[7,9,21]. Regardless of the time of administration, half of the reactions occurred in the first 15 to 20 minutes from the start of the infusion, which coincides with what has been observed in other groups and supports the importance of frequent clinical monitoring of patients in this period and then serially throughout the infusion[12,21]. Kloos et al. demonstrated that non-antibody-mediated reactions occurred later[38].

This study has limitations since it includes only one hospital, which although it is a national reference and referral center in pediatric oncology, may not be completely representative. On the other hand, it is a retrospective study, so the data registry could be incomplete. To minimize this point, medical, nursing, and pharmacy records were reviewed and compared in order to obtain the most reliable data possible. Finally, neither the presence of anti-ASP antibodies nor ASP activity was measured, since both assessments are not yet available in our country.

It could be useful to carry out a prospective multicenter study in which ASP activity and anti-ASP antibody titers are measured, which would allow the diagnosis of silent inactivation and the detection of non-antibody-mediated reactions, providing objective elements for making decisions on switching to second- or third-line therapies or definitively suspending treatment.

In conclusion, with this study, it was possible to determine the incidence of HSR to ASP leading to discontinuation of treatment, both for newly diagnosed ALL and relapsed ALL. The detection and active management of HSR are essential given the high proportion of anaphylaxis observed. The maintenance of ASP treatment during intensive chemotherapy suggests a better prognosis in patients with ALL, showing the importance of an adequate transition from one formulation to another. Further studies are needed to determine the optimal doses and schedule to develop protocols with the lowest incidence of HSR and the highest possible therapeutic effectiveness.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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