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A Profile of the Adverse Effects of Antineoplastic Agents for the Treatment of Children with Cancer

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ABSTRACT

Background: No pharmacovigilance studies of the effects of oncology drugs in children with cancer have been conducted to date in Mexico. The aim of this study is to identify severe adverse drug reactions (ADRs) to oncology drugs in this population. **Material and methods:** Ten medical institutions across the nation that are accredited for the treatment of children with cancer under the "Seguro Popular" health insurance program were included. A 12-month prospective, observational, multicenter study was designed. The association between oncology drugs for the treatment of childhood cancer and severe ADRs was evaluated. The cause for every adverse reaction was determined. **Results:** Nine thousand eight hundred and eleven reports in 1,468 children were received. The mean age was 7.6 ± 0.3 years. High-risk acute lymphoblastic leukemia accounted for 68.1% of the cases. Eigthen thousand eigth hundred and thirty six administration of 24 antineoplastic agents were reported. Four hundred and sixty nine severe ADRs associated with 12 drugs occurred in 133 (9.0%) children. Hematologic toxicities were the most frequent; 93.7% of reactions are described as being possibly drug-related. There were 12 cases of pancreatitis following the administration of L-asparaginase. 58.1% of the reactions were related to three drugs: cytarabine (29.2%), methotrexate (18.1%) and L-asparaginase (10.8%). Five patients died because of myelosuppression associated with daunorubicin (2), septic shock caused by cyclophosphamide (1) and pancreatitis following the administration of L-asparaginase (2). **Conclusions:** The administration of 18,836 doses of oncology drugs was recorded at 10 pediatric hospitals. The study has no doubt contributed to Mexico's Pharmacovigilance program for oncology drugs; severe reactions were reported to the National Pharmacovigilance Center (NPC). (J CANCEROL. 2015;2:7-14)

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INTRODUCTION

According to the National Patient Registry in the "Seguro Popular" health insurance program, the incidence of cancer among children and adolescents aged 0 to 18 years was 150.3 per million in 2010. In that same year, there were 2,403 new cancer cases among patients under the age of 18. In Mexico the prevalence of this group of diseases in the pediatric population (< 18 years) accounts for 7% of all malignant disease in the general population, which is probably a higher rate than that in some industrialized countries[1]. Between 2007 and 2010 the "Seguro Popular" System records show that there were 8,936 children with cancer. It is necessary to use chemotherapy in the treatment for children although these drugs may cause many patients to have severe adverse reactions[2].

Therefore the safety of the drugs prescribed is a public health issue given the adverse drug reactions (ADRs) that can occur[3]. ADRs in children may cause significant morbidity and mortality and result not only in admission to hospital or a prolonged hospitalization, but also in permanent disability and death[4]. Of the 2,258 reports of ADRs made by Mexico to the Center for International Drug Monitoring (the Uppsala Monitoring Center [UMC]) up to 2006, only 238 (9%) were in children under 16 years old, 113 of which occurred in children between the ages of 2 months and 4 years[5].

There have not been many studies in this population so the safety and tolerability of many pharmacological agents is not well established. Often the pharmacological actions of drugs in children are not similar to those identified for adults so therefore information obtained from research in the adult population cannot be applied directly to children[6]. Considering the impact ADRs have on morbidity and mortality rates and the potential vulnerability of children to experiencing ADRs, especially when they are hospitalized, studies to assess the incidence and nature of ADRs in the pediatric population are essential[7].

The purpose of this study was to identify severe ADRs associated with antineoplastic agents in children with acute leukemias, lymphomas and primary tumors of the central nervous system.

MATERIAL AND METHODS

The study was conducted in the pediatric oncology services at 10 hospitals accredited by the "Seguro Popular" health insurance program in nine cities throughout the country. Active pharmacovigilance methods (intensive monitoring) were adopted. Patients between the ages of 0 and 18 years, who were undergoing intravenous chemotherapy treatment and had a confirmed diagnosis of acute leukemia (acute lymphoblastic leukemia and acute myeloid leukemia), lymphoma (Hodgkin's lymphoma and non-Hodgkin's lymphoma) or primary CNS tumors (medulloblastoma and astrocytoma) were enrolled and treated in accordance with chemotherapy protocols approved by the Board of Health.

From November 2010 to October 2011 patients were monitored intensively at each center during administration of chemotherapy and at follow-up visits by a pediatric hematologist or oncologist and a nurse qualified to identify ADRs. Severe ADRs were established by physical examinations and interviews with the patients and their families, as well as by clinical tests and results. Suspected severe ADRs were documented on an instrument designed for this purpose. All demographic and illness-related data were recorded as well as data on the medications that each patient received before the onset of the adverse reaction, including dosage, route of administration, frequency, date of developing the reaction and allergies to food or drugs, in addition to other comorbidities. The reactions were coded using World Health Organization Adverse Drug Reaction Terminology (WHO-ART) and the probability scales described in Mexican Official Standard NOM-220-SSA1-2002 and the modified Naranjo algorithm for causality assessment[19,29]

After being enrolled, patients were monitored for four weeks after they stopped receiving chemotherapy. The severity (intensity of clinical manifestations) of the ADRs was classified on a scale of 1-4, as per WHO classification. For the purposes of the study, only grade 3 reactions, which are classified as severe or medically significant, requiring hospitalization or increased the hospital stay, disabling or limiting self-care and grade 4 reactions, which are classified as life-threatening, with extreme limitation of activities or requiring urgent medical intervention, were taken into account. The study was conducted in accordance with Good Clinical Practice (GCP) and followed Mexican rules and regulations. The coordinators of the study, two experts in hematology/oncology, confirmed the causality of the ADRs.

A qualified independent research organization was responsible for receiving, capturing and reporting the ADRs to the National Pharmacovigilance Center (NPC), as provided by the aforementioned Mexican Official Standard NOM-220-SSA1-20002, except for serious ADRs that occurred at the Hospital Infantil de México and the Hospital Infantil de Morelia "Eva Sámano", which were reported by the pharmacovigilance centers at these institutions. A descriptive analysis was made of the demographic variables and medical histories, as well as of the severe adverse reactions seen among the patients enrolled in the study. Statistical software STATA version 12.0 (StataCorp, TX, USA) was used. The level of statistical significance was set at $p < 0.05$.

RESULTS

During the 12 months of the study, the 10 centers enrolled 1,468 children with the malignancies selected and 18,836 intravenous administration of 24 antineoplastic agents that were prescribed in accordance with Board of Health approved treatment regimens, were recorded. The most commonly used cytotoxic drugs were methotrexate, cytarabine, vincristine, and L-asparaginase, which together accounted for 71.4% of the total injections that were administered (Table 1). The mean age of the study population was 7.6 ± 4.3 years, with a range from 0 to 18 years. 61.1 % of patients were aged between 4 and 12 years. The male to female ratio was 1.4:1. Most of the male patients were diagnosed with acute lymphoblastic leukemia (89.1%) (Table 2).

Table 1. Antineoplastic agents used and number of injections (n = 18,836)

	Antineoplastic agents	Number of injections	%
1	Methotrexate	4,797	25.4
2	Cytarabine	4,021	21.3
3	Vincristine	2,683	14.2
4	L – Asparaginase	1,991	10.5
5	Etoposide	1,649	8.7
6	Cyclophosphamide	1,099	5.8
7	6 – Mercaptopurine	674	3.5
8	Doxorubicin	651	3.4
9	Daunorubicin	501	2.6
10	Bleomycin	140	0.7
11	Vinblastine	130	0.7
12	Ifosfamide	127	0.6
13	Dacarbazine	120	0.6
14	Carboplatin	115	0.6
15	Temozolomide	47	< 0.5
16	Mitoxantrone	36	< 0.5
17	Nimotuzumab	15	< 0.5
18	Clofarabine	12	< 0.5
19	Rituximab	8	< 0.5
20	Idarubicin	8	< 0.5
21	Cisplatin	6	< 0.5
22	Imatinib	3	< 0.5
23	Actinomycin D	2	< 0.5
24	Fludarabine	1	< 0.5

It was reported that 133 children (9%) experienced a severe ADR during the study. No significant difference in the gender distribution of ADRs ($p = 0.09$) was found. The age group most affected was that of children aged 4-12 years (60.9%). 66.9% (89) of the patients who had a severe ADR had high-risk acute lymphoblastic leukemia, 10.5% (14) had acute myeloid leukemia and 7.5% (10) had non-Hodgkin's lymphoma. A total of 469 severe ADRs were reported; these were associated with 12 antineoplastic

Table 2. Demographic and clinical characteristics of the cohort of children (n = 1,468)

	Number of patients	%
Sex		
– Male	856	58.3
– Female	612	41.7
Age		
– < 1 year	14	0.9
– 1-3 years	283	19.3
– 4-12 years	896	61.1
– 13-15 years	204	13.9
– 16-18 years	71	4.8
Diagnosis		
– Acute lymphoblastic leukemia (average risk)	223	15.3
– Acute lymphoblastic leukemia (high risk)	989	67.4
– Acute lymphoblastic leukemia (very high risk < 1 year)	28	1.9
– Acute myeloid leukemia	72	4.9
– Hodgkin's lymphoma	48	3.3
– Non-Hodgkin's lymphoma (includes Burkitt's type)	30	2.0
– Lymphoblastic lymphoma	29	1.9
– Large B-cell lymphoma	3	0.2
– Medulloblastoma	25	1.7
– Astrocytoma	21	1.4
History of allergy to food or drugs		
– Yes	72	4.9
– No	1,396	95.1

agents; more than half of the reactions were related to cytarabine (29.2%), methotrexate (18.1%) and L-asparaginase (10.8%) (Fig. 1).

Fifty four percent of the ADRs were classified as grade 3 and 46% as grade 4. Using the Naranjo algorithm, 88% were considered to be possibly related to the cancer drug. 74.4% (349) of the ADRs were hematologic, of which 75.4% were classified as grade 4 and 93.7% were related to the antineoplastic agent that was administered. Gastrointestinal disorders were the second most common type and accounted for 11.3% (53) of the ADRs, 64.2% were classified as grade 3 and 86.7% were considered to be possibly related to the antineoplastic agent. Twenty four infectious events (5.1%) were documented, 58.3% were grade 4 and 91.7% were possibly related to the cytotoxic drugs (Table 3).

There were seven fatal reactions associated with these drugs: a child presented with grade IV myelosuppression associated with daunorubicin; septic shock was associated with cyclophosphamide in two cases; three patients presented with pancreatitis after administration of L-asparaginase and

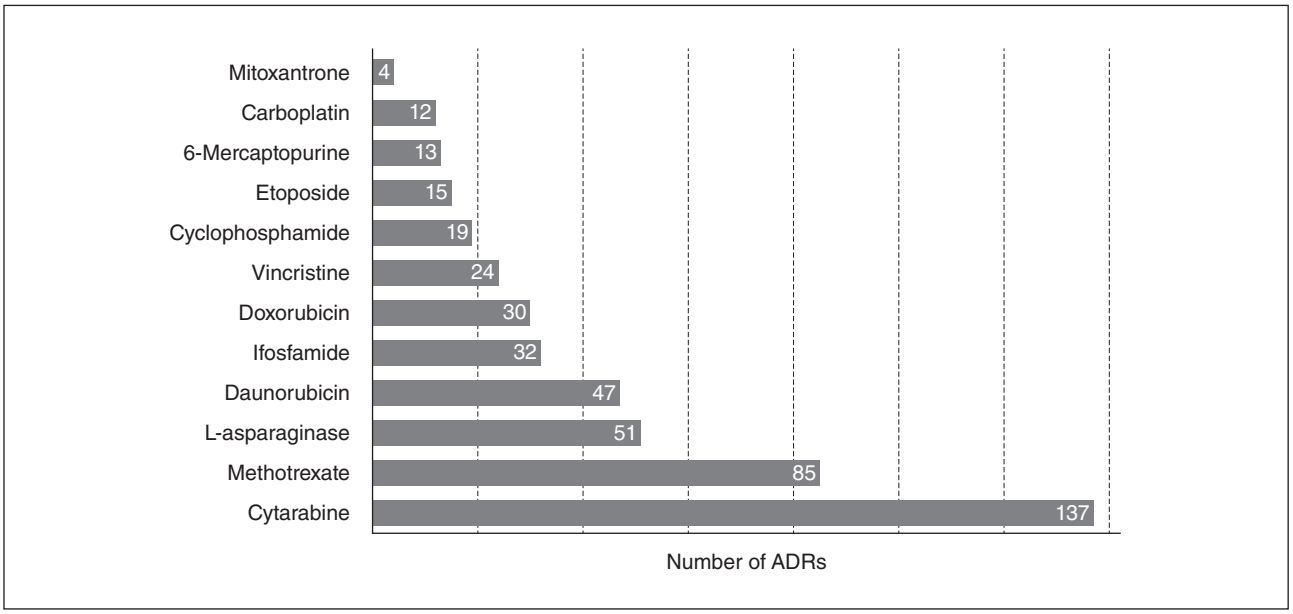

Figure 1. Number of severe ADRs associated with antineoplastic agents (n = 469).

Table 3. Type of severe ADR reported per system or organ class, including grade and causality (n = 469)

Disorders	Frequency n (%)	Grade		Causality	
		3	4	Possible	Probable
Hematologic					
– Anemia	23 (6.5)	15	8	23	0
– Lymphopenia	28 (8.0)	7	21	27	1
– Myelosuppression	6 (1.4)	1	5	6	0
– Neutropenia	210 (31)	38	172	195	15
– Thrombocytopenia	82 (23.4)	25	57	76	6
	349 (100%)	86 (24.6%)	263 (75.4%)	327 (93.7%)	22 (6.3%)
Gastrointestinal					
– Appendicitis	1 (1.8)	1	0	1	0
– Neutropenic enterocolitis	19 (35.8)	11	8	17	2
– Diarrhea	1 (1.8)	1	0	1	0
– Paralytic ileus	1 (1.8)	1	0	1	0
– Mucositis	14 (26.4)	14	0	14	0
– Nausea	2 (3.7)	2	0	1	1
– Pancreatitis	12 (22.6)	1	11	8	4
– Gastrointestinal bleeding	1 (1.8)	1	0	1	0
– Vomiting	2 (3.7)	2	0	2	0
	53 (100%)	34 (64.2%)	19 (35.8%)	46 (86.7%)	7 (13.3%)
Infections					
– Oral candidiasis	1 (4.2)	1	0	1	0
– Septic shock	15 (63)	4	11	15	0
– Pneumonia	3 (12.5)	2	1	1	2
– Sepsis	5 (20.8)	3	2	5	0
	24 (100%)	10 (41.7%)	14 (58.3%)	22 (91.7%)	2 (8.3%)
General					
– Hypovolemic shock	1 (4.3)	0	1	1	0
– Fever	22 (95.6)	16	6	22	0
	23 (100%)	16 (69.6%)	7 (30.4%)	23 (100%)	–
Hepatobiliary system					
– Hyperbilirubinemia	2 (50)	0	2	2	0
– Transaminase elevation	2 (50)	1	1	2	0
	4 (100%)	1 (25%)	3 (75%)	4 (100%)	–
Musculoskeletal system					
– Muscle weakness	1 (100)	1	0	1	0
	1 (100%)	1 (100%)	–	1 (100%)	–
Skin and subcutaneous tissue					
– Cellulitis (finger, leg)	2 (50)	1	1	2	
– Exfoliative dermatitis	1 (25)	0	1	1	0
– Dermatosis	1 (25)	1	0	1	0
	4 (100%)	2 (50%)	2 (50%)	4 (100%)	–
Respiratory system					
– Shortness of breath	1 (100)	1	0	1	0
	1 (100%)	1 (100%)	–	1 (100%)	–
Renal and urinary system					
– Acute kidney injury	1 (50)	1	0	1	0
– ADH* Secretion	1 (50)	1	0	1	0
	2 (100%)	2 (100%)	–	2 (100%)	–
Immune system					
– Allergic reaction	1 (100)	1	0	1	0
	1 (100%)	1 (100%)	–	1 (100%)	–
Nervous system					
Sensory impairment	1 (14.2)	1	0	1	0
– Neuropathic pain	1 (14.2)	1	0	1	0
– Dizziness	1 (14.2)	1	0	1	0
– Neuropathy	1 (14.2)	0	1	1	0
– Neurologic toxicity	2 (28.5)	1	1	2	0
– Cortical disorder	1 (14.2)	0	1	1	0
	7 (100%)	4 (57.2%)	3 (42.8%)	7 (100%)	–

*ADH: Antidiuretic hormone

Table 4. Fatal ADRs (n = 7)

	Patient initials	Age in years	Sex	Diagnosis	Antineoplastic agent	Adverse Reaction	Grade	Modified Naranjo Causality
1	TGTG	9	F	High risk acute lymphoblastic leukemia	Daunorubicin	Myelosuppression	4	Possible
2	AMMC	3	F	Non-Hodgkin's lymphoma	Cyclophosphamide	Septic shock	4	Possible
3	BLE	10	M	Large B-cell lymphoma	Cyclophosphamide	Septic shock	4	Possible
4	AAL	14	F	High risk acute lymphoblastic leukemia	L-Asparaginase	Pancreatitis	4	Possible
5	BPJ	12	M	High risk acute lymphoblastic leukemia	L-Asparaginase	Pancreatitis	4	Possible
6	BARC	15	F	High risk acute lymphoblastic leukemia	L-Asparaginase	Pancreatitis	4	Probable
7	MBA	< 1	M	High risk acute lymphoblastic leukemia	Cytarabine	Neutropenic enterocolitis	4	Probable

a child with myelosuppression presented with neutropenic enterocolitis secondary to cytarabine (Table 4).

DISCUSSION

Pharmacovigilance is essential to evaluated the efficacy and safety of chemotherapy in the medium and long term since in most cases the drugs can cause adverse events[8-10].

This type of research in children should be a priority, considering that clinical research trials that test new drugs in pediatric patients are generally based on smaller samples than studies in adults, so they may over- or underestimate some of the positive and negative impacts. It is also known that given the maturation, growth and development of children, information regarding pharmacokinetics is difficult to reproduce especially when a patient has other comorbidities[11-13]. Lastly, there are disorders associated with growth and development in children that are not seen in adults. Premarketing clinical studies are focused on the efficacy of the drugs and their short-term safety, especially in oncology, so that their effects in the medium to long term turn out to be a secondary objective[14-16].

The results of this active monitoring in children with cancer at 10 pediatric hospitals showed that 9% of the patients who were enrolled had severe ADRs. In Mexico there is little literature on pharmacovigilance in pediatric oncology, which makes it difficult to compare this finding with those of other countries or institutions[17-19].

In pediatrics in general the reported incidence of ADRs is low[20]. In an active monitoring study conducted in 2009, Clavenna reported the presence of ADRs in 15 out of 1,000 children overall, which gives a rate of 1.5%[21]. This difference in oncology drugs is to be expected given the toxic potential of chemotherapeutic agents.

Adverse drug reactions in children described in the literature affect mainly the skin (rash and urticaria), the gastrointestinal system (diarrhea, nausea and vomiting) and a few that affect the central nervous system[22-24]. The percentage of ADRs related to chemotherapeutic agents generally refers to adults and vary according to the drug used[25-27].

In this study, the population was selected at random and over 90% turned out to have acute lymphoblastic leukemia. The drugs most frequently associated with severe ADRs were the drugs used

in the treatment of this disease, basically methotrexate, L-asparaginase and cytarabine.

The most common toxicity was myelosuppression, mainly anemia, lymphopenia and thrombocytopenia. This is a non-specific toxicity and it is difficult to attribute it to any single drug as even the steroids that are a component in the treatment of leukemia can cause it. Nevertheless, on the basis of the Naranjo algorithm, which takes into account the dose, time and comorbidities, causality was established[28].

In this study 12 patients presented with pancreatitis, which is an adverse event commonly associated with the use of L-asparaginase, three of which resulted in death. This is a higher rate than that reported in the literature[29]. In Mexico, the natural form is used and only the formulation containing E. coli-derived L-asparaginase is commercially available. In the Rawlins and Thompson classification this is a type A reaction as it involves anaphylaxis, in contrast with the pathophysiology of other drugs, where the effects are directly related to the dose[30].

With regard to causality, most of the reactions were possible given the concept of polypharmacy that is used in the treatment of pediatric oncology patients.

The biases of this study are related to several factors. The first is that within the selection criteria only children with severe ADRs were included, increasing the likelihood of fatal events.

Nor did we select a balanced sample of patients so it turned out that nearly all of the patients had leukemia and we were unable to explore the toxic potential of drugs used to treat Hodgkin's lymphoma, such as dacarbazine, or those used in brain tumor treatment, such as temozolomide.

This work is a first step towards tackling an issue that affects all children with cancer and that has not yet been studied in Mexico. Future goals are to extend the analysis to all malignant neoplasms, including more hospitals and lastly to integrate this effort into a systematic approach.

Pharmacovigilance studies that assess the "normal" use of drugs both quantitatively and qualitatively are required and it is necessary to promote a culture in this regard both in hospitals and doctors' offices with the aim of analyzing the population at large. In future these data will allow us to provide the patients and their parents with information that has been scientifically proven about quality of life during and after treatment, possible long term effects and will allow us to complete Phase IV clinical trials as established.

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