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Acute and sub-acute neurological toxicity in children treated for acute lymphoblastic leukemia

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ABSTRACT

Eighty percent of children with acute lymphoblastic leukemia (ALL) survive with current treatments. Neurotoxicity is an infrequent adverse event. We describe clinical presentations of neurological toxicity, phases of treatment when these adverse events were more frequent and patients´ outcome.

From January-1995 to December-2015, 1379 ALL cases were admitted. Neurotoxicity was diagnosed in 49 patients (3.6%) and classified according to neurological syndromes. Medical records, laboratory-tests and images were reviewed. The diagnosed syndromes were: a) Methotrexate-leukoencephalopathy (MLE) (35.4%); b) Cerebral-venous-sinus thrombosis following L-Asparaginase administration (26.5%); c) Vincristine-induced-vocal-cord paralysis (VVCP) (14.2%); d) Stroke-associated vasospasm (14%), after high-dose methotrexate e) Severe polyneuropathy (6.1%); f) Methotrexate myelopathy (2%); and g) *Pseudotumor-cerebri* (2%) associated with corticosteroid therapy. Neurotoxicity was diagnosed during induction in 55% of cases.

We conclude that MLE was the most frequent syndrome. VVCP was observed in infants and Down patients. Seizure was the most common symptom and toxicity occurred mainly during induction phase.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Treatment results in childhood ALL are one of the true success stories of modern clinical oncology, with an overall cure rate of 80% with the administration of intensive multiagent chemotherapeutic regimens [1]. High dose chemotherapy and central nervous system (CNS) directed therapy has become a prerequisite for successful of ALL treatment childhood [1]. Before its introduction between late 1960s and early 1980s, more than 25% of children with ALL suffered from disease recurrence originated in the CNS [2]. This rate could be reduced to less than 5% through the introduction of cranial irradiation, intrathecal (i.t.) chemotherapy with methotrexate alone or in combination with other drugs (cytarabine, corticosteroid) and systemic application of chemotherapeutic agents with adequate penetration into the CNS (high-dose methotrexate, dexamethasone, high-dose cytarabine) [2]. The intensity of CNS-directed treatment has been adjusted according to the risk of developing relapses in CNS and one of the most important identified risk factor is CNS involvement at diagnosis (currently defined as CNS3) [3]. Additional risk factors include a higher initial white blood cell count, pro-B or precursor T-cell immunophenotype, t(9;22) or t(4;11), and a traumatic lumbar puncture (LP) with identifiable blast cells present at diagnosis (event resulting from traumatic LP) [3,7]. CNS- directed therapy may differ in the number of i.t. injections and/or intrathecal- applied drugs, as well as in the inclusion of different doses of cranial irradiation according to different treatment philosophies and the evolution of protocols. Most current protocols administer intensive systemic therapy; however, preventive cranial irradiation is still recommend for high-risk patients and/or some ALL with a precursor T-cell immunophenotype [4,7], excluding infants (children younger than 1 year of age). Patients with traumatic LP have been recommended to receive additional therapeutic doses of i.t. chemotherapy [4]. Besides, patients with CNS compromise receive more intensive i.t. chemotherapy and, treatment also includes cranial irradiation (18 or 24 Gy when the patients are older than two years of age; younger children should receive reduced doses) [4], in most current protocols. However, the tendency in current studies is to reduce the indication of radiotherapy, based on recent retrospective analysis [8]

The intensification of treatment and CNS-directed therapy result in an increased risk of toxicity. CNS toxicity used to be a cause of limiting or withdrawing therapy in severe cases. But other neurological

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Table 1
Local treatment the CNS, differences according to each protocol.

Protocols	MTX (IV) Dose/m2	Lumbar Puncture		Radiotheraphy Dose	
		N°	MTX-TIT	Prophylactic CNS 1-2	Therapeutic CNS 3
ALL 90-GATLA	2 G/M2	9	TIT	1200 cGy	1800 cGy
ALL-96 BFM HPG	5 G/M2 (SR-MR)	11+(4)	MTX	1200 cGy	1800 cGy
	5 G/M2 (HR)	11+(5)	MTX 5+(3) TIT 6+(2)		
ALLIC BFM 02	BCP 2 G/M2(SR-MR)	15+(5)	MTX	1200 cGy	1800 cGy
	TCP 5 G/M2	15+(5)	MTX		
	BCP 5G/M2 (HR)	14+(6)	MTX 11+(5) TIT 3+(1)		
ALLIC BFM 09	BCP(SR-MR) R 2 G/M2	15+(5)	MTX		1800 cGy
	5 G/M2	11+(5)	MTX		
	BCP- TCP (HR) 5G/M2	13+(6)	MTX 7+(5) TIT 6+(6)	1200 cGy	1800 cGy
	TCP (MR) 5G/M2				
	<100000 WBC	17+(5)	MTX		
	>100000 WBC	11+(5)	MTX	1200 cGy	1800 cGy
INTERFANT-99	5 G/M2	12+(2)	MTX(7)+ DEXA- 5 DIT		
INTERFANT-06	5 G/M2	12+(2)	MTX(7)+ DEXA- 5 DIT		

Note: MTX: Methotrexate; TIT: Triple intrathecal with methotrexate, cytarabine and dexamethasone; SR: Standard risk; MR: Medium risk; HR: High risk; R: Randomization; WBC: White blood cell; DTI: Double intrathecal with cytarabine and dexamethasone.

complications, such as cerebral-venous-sinus thrombosis following L-Asparaginase administration, Vincristine-induced-vocal-cord paralysis (VVCP), stroke-associated vasospasm after high-dose methotrexate, polyneuropathy and *Pseudotumor-cerebri* may also appear during ALL therapy.

Our aims were to describe the signs and symptoms of neurological toxicity of any kind observed in ALL patients in our center, to assess symptoms, to define which phases of treatment presented an increased risk of developing and the drugs related to this toxicity and to describe the outcome of different neurological syndromes and their outcome and long term sequelae.

2. Material and methods

From January 1995 to December 2015, 1379 patients were diagnosed and treated as ALL in the Hematology and Oncology Department at Hospital de Pediatría Prof. Dr. Juan P. Garrahan.

Database of ALL was analyzed in order to detect cases who presented neurological toxicity and the records of these cases were retrospectively analyzed for defining clinical presentation, reviewing images and describing the outcome of neurological complications and *sequelae*.

Neurological symptoms and signs related to treatment were diagnosed in 49 patients (3.55%), who were grouped according to the initial neurological syndromes. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 3.0) (Tables 2a–b, 3a–b, 4a–b).

CNS status was defined according to the number of cells in the first LP and the presence or not the blasts. CNS 1 was defined in cases with less than 5 cells/mm^3without blasts. CNS 2 were cases with less than 5 cells/mm^3but with presence of blasts or traumatic LP and CNS 3 was defined in cases with more than 5 cells/$mm^3$and with confirmation of presence of lymphoblast, cranial nerve palsy, or presence of CNS mass observed by images.

During the analyzed period, patients were registered in 6 different protocols: LLA 90–GATLA [5], LLA96 BFM-HPG [3], ALLIC-BFM 02 [7] and the ongoing ALLIC- BFM 2009 protocol. In addition, since 1999 patient younger than 1 year of age were treated according Interfant-99 and Interfant-06 [6] protocols. The CNS-treatment administered was different in each protocol and it is described in Table 1.

Medical records, laboratory tests and images of this group of patients were reviewed in order to define the relationship between symptoms and administered chemotherapy.

2.1. Treatment schedules

Different treatment strategies were administered to in the patients included in this study, with different doses of chemotherapy according to different protocols.

One patient was included in the LLA 90-GATLA protocol [5]. In this study, the patients received MTX system at 2 gr/m^2. The CNS-directed