HDMTX en tumores sólidos y hematológicos: Intoxicación.

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Dr. J.L. Dapena, Dr. F.J. Bautista.

Estrategias para la mejora del tratamiento con dosis altas de metotrexato: la farmacocinética clínica como herramienta para la optimización de la eficacia y toxicidad.

19 de octubre de 2015

HDMTX en tumores sólidos y hematológicos: Intoxicación.

Dr. José Luis Dapena.

- **Factores predictivos de una intoxicación por MTX**
- **Tipo de paciente en que debo incrementar la alerta**
- **Parámetros clínicos que influyen en la eliminación del MTX**

Factores de riesgo para el retraso en la eliminación

- Interacciones farmacológicas
- Tercer espacio
- Nefrotoxicidad directa por metotrexato
- Inadecuada hidratación/alcalinización
- Síndrome de Down

Perazella MA, Moeckel GW (2010). Nephrotoxicity from chemotherapeutic agents: clinical manifestations, pathobiology, and prevention/therapy. Semin Nephrol 30:570-581

Widemann BC, Adamson PC (2006). Understanding and managing methotrexate neprhotoxicity. The Oncologist 11:694-703

Factores de riesgo: interacciones farmacológicas

Fármacos que pueden disminuir la eliminación de metotrexato

- AINEs
- Penicilinas
- Inhibidores de la bomba de protones: omeprazol
- Anfotericina
- Utilización previa de análogos del platino
- Otros: probenecid, gemfibrocilo, imatinib…

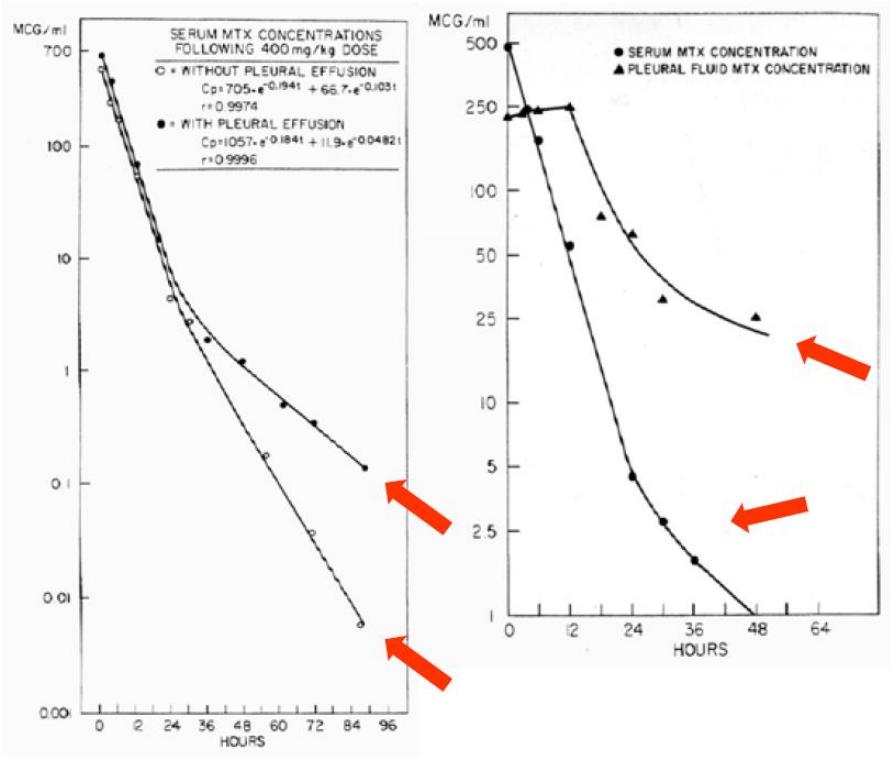
Perazella MA, Moeckel GW (2010). Nephrotoxicity from chemotherapeutic agents: clinical manifestations, pathobiology, and prevention/therapy. Semin Nephrol 30:570-581

Widemann BC, Adamson PC (2006). Understanding and managing methotrexate nephrotoxicity. The Oncologist 11:694-703

Hammor and Hasan, (2013). J Cancer Sci Ther 5(3) 106-112.

Factores de riesgo: tercer espacio (derrame pleural, ascitis)

Vida media plasmática prolongada MTX → mayor exposición a MTX → incremento del riesgo de toxicidad (puede ser rescatado con ácido folínico)



Fox RM (1979) Methotrexathe neprotoxicity. Clin Exp Pharmacol Physiol. Suppl 5, 43-45

Dr. Dapena

Factores de riesgo: nefrotoxicidad por metotrexato

- Obstrucción renal secundaria al depósito de cristales de MTX y sus metabolitos (17-OH-metotrexato) en los túbulos renales
- Toxicidad directa del fármaco sobre estos túbulos

High-dose methotrexate: on the relationship of methotrexate elimination time vs renal function and serum methotrexate levels in 1164 courses in 264 Swedish children with acute lymphoblastic leukemia (ALL). Cancer Chemother Pharmacol. 2003 Apr;51(4): 311-20

PURPOSE:
The objectives of the present study were to determine the relationship between methotrexate (MTX) elimination time and various aspects of renal function and to evaluate the prognostic value of elevated serum MTX and creatinine for delayed MTX elimination.
PATIENTS AND METHODS:
The majority of the 264 children were being treated for ALL. According to the NOPHO-92 protocol, 5 or 8 g MTX/m(2) was administered over 24 h. Serum creatinine was assessed daily. In 11 patients from one centre, renal function was studied in more detail using serum cystatin C, iohexol clearance, and urinary albumin, IgG and protein HC.
RESULTS:
Increased serum creatinine correlated significantly with the elimination time of MTX, whereas no indications were found of tubular or barrier function damage. Of the 1164 courses, 44 had delayed elimination of MTX (>/=120 h). Serum MTX >150 microM at the end of infusion had a sensitivity of 0.27 and a specificity of 0.94 to predict delayed MTX elimination, and >/=50% increase in serum creatinine during the first treatment day (creatinine ratio) had a sensitivity of 0.32 and a specificity of 0.99. The corresponding risk ratios were 5 and 19 for MTX >150 micro M and creatinine ratio, respectively. In courses with a normal elimination time (<72 h), 99% of the courses had a rise in serum creatinine of less than 50%.
CONCLUSIONS:
Elevation of serum creatinine by more than 50% is a better predictor of delayed elimination than the level of serum MTX at the end of MTX infusion, especially if information on previous creatinine measurements is used to reduce the impact of an occasionally low serum creatinine value before the start of the MTX infusion.

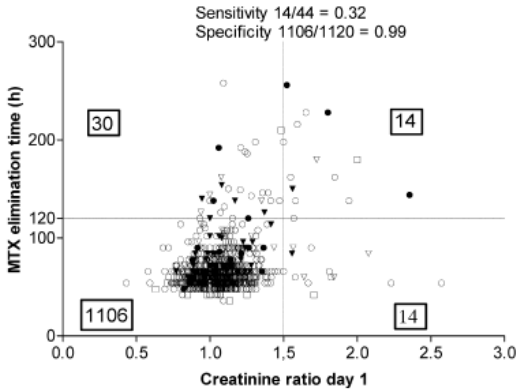


Fig. 7 S-creatinine ratios day 1 (S-creatinine measured 12–24 h after the start of MTX infusion divided by that before the start of the course) and MTX elimination time in 1164 courses administered to 264 patients. The numbers indicate the number of courses in each region of the Figure (■ □ <4 g MTX/m^2, ● ○ ≥4 g and <7 g MTX/m^2, ▼ ▽ ≥7 g MTX/m^2; □ ○ ▽ MTX C_{23} ≤150 μ*M*, ■ ● ▼ MTX C_{23} >150 μ*M*)

Perazella MA, Moeckel GW (2010). Nephrotoxicity from chemotherapeutic agents: clinical manifestations, pathobiology, and prevention/therapy. Semin Nephrol 30:570-581
Yarlagadd SG and Perazella MA (2008). Drug-induced crystal nepropathyMn update. Expert Opinion on Drug Safety, 7, 147-158.
Widemann BC, Adamson PC (2006). Understanding and managing methotrexate nephrotoxicity. The Oncologist 11:694-703

Dr. Dapena

Assessment of renal function during High-Dose Methotrexate Treatment in children with acute lymphoblastic leukemia. Ylinen E et al. Pediatr Blood Cancer 2014 Dec;61(12):2199-202

BACKGROUND:
High-dose methotrexate (HD-MTX) is potentially nephrotoxic. The feasibility of novel biomarkers to indicate renal injury due to HD-MTX infusion was studied in children with acute lymphoblastic leukemia (ALL).

PROCEDURE:
Markers for glomerular and tubular injury were evaluated prospectively after HD-MTX infusion in 20 children with ALL. Plasma creatinine, cystatin C, and neutrophil gelatinase-associated lipocalin (NGAL) were measured 24-48 hr before MTX-infusion and 24, 36, 48, and 72 hr after starting the HD-MTX treatment, and thereafter daily until the MTX concentration was below 0.1 μmol/L. Urine NGAL, β2 -microglobulin, and creatinine concentrations as well as dipstick and urinalysis were performed at the same time points.

RESULTS:
In children with ALL, HD-MTX treatment at 5 g/m(2) over 24 hr was well tolerated and none of the patients developed significant glomerular or tubular dysfunction. The mean plasma cystatin C level increased significantly ($P < 0.001$) from 0.83 mg/L at baseline to 0.94 mg/L at 36 hr after starting the HD-MTX treatment. The cystatin C concentration remained within reference range in all but two patients (10%). There was no significant change in plasma creatinine level during or after HD-MTX treatment, the values being normal in all patients. Plasma and urea NGAL did not increase during or after the HD-MTX treatment.

CONCLUSIONS:
Our results suggest that plasma cystatin C concentration alone is a sensitive marker to monitor renal function during and after HD-MTX infusion in pediatric ALL patients. Plasma or urine NGAL do not provide any further advantage in the follow-up of these patients.

TABLE II. Mean (95% Confidence Interval) Plasma Creatinine, Cystatin C and Methotrexate Concentration at Baseline and 24, 36, 48, and 72 hr After Starting MTX Infusion and the Presence of Abnormal P-NGAL or Urine Findings at Same Time Points

	Baseline	24 hr	36 hr	48 hr	72 hr	*P*-value
PCr (mg/dL)	0.37 (0.08)	0.38 (0.06)	0.37 (0.06)	0.38 (0.05)	0.36 (0.05)	$P = 0.78$
Cystatin C (mg/L)	0.83 (0.06)	0.83 (0.09)	0.94 (0.09)	0.93 (0.11)	0.88 (0.10)	$P < 0.001$
P-NGAL (μg/L) (>150 μg/L), n	1					
U-NGAL (μg/L) (>92 μg/L), n						
U-β_2-microglobulin (mg/L), n		1				
Microskopic hematuria (E6/L), n	1		2	1		
Pyuria (E6/L), n	2			1		
MTX (μmol/L)		70.8 (11.03)[a]	1.22 (0.32)	0.29 (0.08)	0.08 (0.02)	

PCr, plasma creatinine; NGAL, neutrophil gelatinase-associated lipocalin; MTX, methotrexate; P, plasma; U, urine; n, number. [a]at 23 hr point.

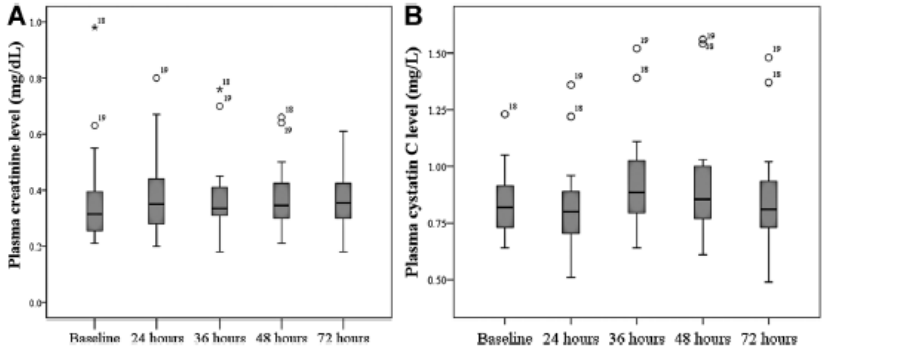


Fig. 1. Box plot showing plasma creatinine level (A) and cystatin C level (B) before and after administration of HD-MTX treatment.

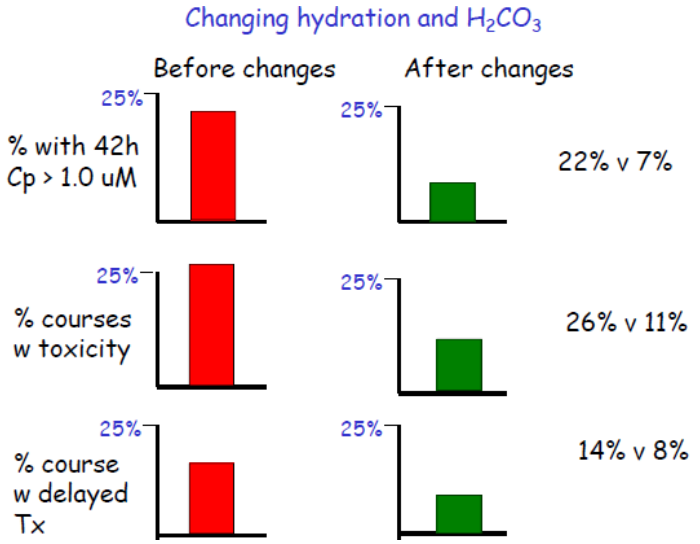
Dr. Dapena

Factores de riesgo: hidratación

Effect of hydration on methotrexathe plasma concentrations in children with acute lymphocytic leukemia. **Christensen ML et al. JCO 1988;6:797-801**

Abstract

Hydration and urinary alkalinization are used with high-dose methotrexate (HDMTX) to minimize renal toxicity resulting from methotrexate (MTX) precipitation in the kidney tubules. The effect of two hydration and alkalinization schedules on MTX plasma concentrations were evaluated in 100 children with acute lymphocytic leukemia (ALL) following two courses of MTX, 2 g/m2. The mean 21- and 44-hour MTX plasma concentrations were significantly lower in the group receiving the greater hydration and alkalinization schedule: 0.79 (0.90 SD) v 1.39 (1.99 SD) mumol/L for 21-hour MTX plasma concentrations, P = .01; and 0.18 (0.38 SD) v 0.25 (0.50 SD) mumol/L for 44-hour MTX plasma concentrations, P = .01. Although the overall incidence of toxic events was similar in both groups, the incidence of severe toxicity was reduced in the group that received the greater hydration and alkalinization, 6% v 16%. This study demonstrated that the amount of hydration and alkalinization can affect MTX plasma concentrations. Optimizing the hydration and alkalinization schedule is important for minimizing the incidence of severe toxicity associated with HDMTX.



Dr. Dapena

Factores de riesgo: hidratación

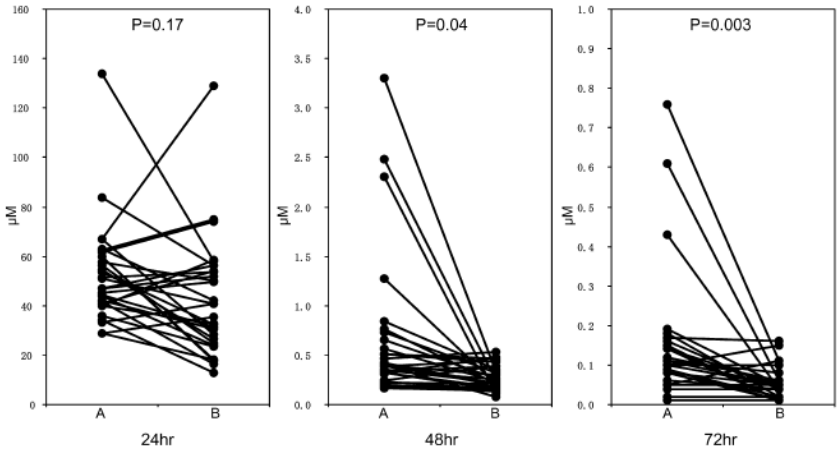
Effects of sodium in hydration solution on plasma methotrexate concentrations following high-dose methotrexate in children with acute lymphoblastic leukemia. Cancer Chemother Pharmacol 2003;51:256-260

PURPOSE:
To test whether a higher sodium dose in the hydration solution may facilitate faster methotrexate (MTX) elimination as compared with a lower sodium dose following high-dose MTX (HDMTX) treatment.

METHODS:
Intravenous solutions with alternate doses of sodium (regimen A 70 mEq/l, regimen B 100 mEq/l) were given to 30 children with acute lymphoblastic leukemia in two courses of HDMTX in a randomized crossover fashion. The plasma MTX concentrations every 24 h from the beginning of MTX administration and the adverse events associated with HDMTX were compared between the two hydration regimens.

RESULTS:
The plasma MTX concentrations were similar in the two hydration regimens at 24 h (A 50.9+/-7.4 vs B 40.9+/-5.4 microM, means+/-SE, P=0.17), but was significantly lower in regimen B at 48 and 72 h (A 0.65+/-0.17 vs B 0.27+/-0.03 microM, P=0.04; and A 0.14+/-0.03 vs B 0.05+/-0.01 microM, P=0.003). The time during which MTX plasma concentrations exceeded 0.1 microM was significantly longer in regimen A than in regimen B (A 3.83+/-0.18 vs B 3.13+/-0.06 days, P=0.001). The incidences of adverse events were similar between the two regimens (P=0.78), and severe adverse events were not seen in either regimen.

CONCLUSIONS:
Hydration with a higher sodium dose facilitated faster MTX elimination following HDMTX. Sodium may have a beneficial effect on MTX-induced nephrotoxicity.



Dr. Dapena

Factores de riesgo: hidratación

Extended duration of prehydratation does not prevent nephrotoxicity or delayed drug elimination in HDMTX infusions: a Prospectively Randomidez Cross-Over Study. Pediatr Blood Cancer. 2014 Feb;61(2):297-301

BACKGROUND:
Alkalized hydration is used as supportive care to prevent renal toxicity during infusions with high-dose methotrexate (HDMTX). In children with acute lymphoblastic leukemia (ALL), the hydration is commonly initiated 4 hours before start of the methotrexate (MTX) infusion. To test if longer duration of prehydration would prevent MTX-induced renal toxicity, we preformed a randomized cross-over study comparing 12-4 hours of hydration before the infusion of HDMTX.

PROCEDURES:
Children with ALL and non-Hodgkin lymphoma that were treated with infusions of HDMTX 5 or 8 g/m(2) were randomized to receive intravenous prehydration 12 or 4 hours before the first HDMTX infusion. Patients alternated between 12 and 4 hours of prehydration in the subsequent HDMTX infusions. Renal toxicity was defined as 50% increase in plasma creatinine after the HDMTX infusion. The plasma MTX concentration was measured during and after the HDMTX infusion to determine if the duration of prehydration would influence the systemic MTX clearance.

RESULTS:
A total of 47 patients (224 HDMTX infusions) with a median age of 4.9 years were included in the study. The duration of prehydration had no effect on MTX induced renal toxicity that occurred in 18.5% of all HDMTX 5 g/m(2) infusions and in 40.0% of all HDMTX 8 g/m(2) infusions. Similar the duration of prehydration had no impact on the systemic clearance of MTX.

CONCLUSION:
Extending prehydration beyond 4 hours does not reduce the risk of renal toxicity or delayed MTX clearance after infusions with HDMTX 5-8 g/m(2).

TABLE I. Demographics and Characteristics of Patients

	Diagnosis	Age (years)	BSA (m^2)	Gender	Number of infusions	
HDMTX dosage	ALL/lymphoma	Median (range)	Median (range)	Female/male	Total	Median (range)
5 g/m^2 (n = 35)	32/3	4.9 (2.0–19.6)	0.78 (0.54–2.23)	15/20	189	5 (2–9)
8 g/m^2 (n = 12)	11/1	5.2 (2.5–19.0)	0.78 (0.60–1.85)	6/6	35	3 (2–4)
Total (n = 47)	43/4	4.9 (2.0–19.6)	0.78 (0.54–2.23)	21/26	224	4 (2–9)

HDMTX, high-dose methotrexate; ALL, acute lymphoblastic leukemia; BSA, body surface areas.

TABLE II. Plasma Methotrexate After 4- and 12-Hour Prehydration (Median and Range)

	HDMTX 5 g/m^2				HDMTX 8 g/m^2			
Plasma PK variable	4-Hour	12-Hour	n	*P**	4-Hour	12-Hour	n	*P**
23-Hour (μM)	85.0 47–209	86.9 44–217	35	0.56	123 57–206	132 49–226	12	0.93
36-Hour (μM)	2.0 0.8–11.7	2.2 0.8–16.4	35	0.64	3.8 1.0–7.5	3.3 1.2–23.4	12	0.27
42-Hour (μM)	0.8 0.3–6.2	0.9 0.3–5.7	35	0.17	1.71 0.4–6.0	1.2 0.5–25.5	12	0.40
AUC	17.8 4.5–132	17.5 6.3–105	35	0.34	33.0 8.6–162	25.4 10–691	12	0.39

TABLE III. MTX Induced Renal Toxicity Assessed as Change in Serum Creatinine After the 4- and 12-Hour Prehydration and 5 g/m^2 Methotrexate (Median and Quartiles)

		HDMTX 5 g/m^2			HDMTX 8 g/m^2		
	Unit	4-Hour	12-Hour	*P**	4-Hour	12-Hour	*P**
Baseline creatinine	μM	36 26–42	34 26–43	0.43	22 18–56	28 19–50	0.75
Change in creatinine[a]	%	22 5–31	19 5–30	0.48	41 22–80	50 15–98	0.63

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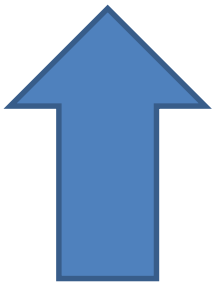
Factores de riesgo: alcalinización

La solubilidad del metotrexate y sus metabolitos (7-OH-MTX y DAMPA) es pH dependiente

pH	Solubilidad
6.9	22 mM
6.3	9 mM
5.7	2.2 mM



Un incremento en el pHo de 6 a 7, aumenta la solubilidad del MTX y sus metabolitos 5-8 veces

Perazella MA, Moeckel GW (2010). Nephrotoxicity from chemotherapeutic agents: clinical manifestations, pathobiology, and prevention/therapy. Semin Nephrol 30:570-581

Widemann BC, Adamson PC (2006). Understanding and managing methotrexate neprhotoxicity. The Oncologist 11:694-703

Hyperalkalinization without hyper-hydratation for the prevention of high-dose methotrexate acute nephrotoxicity in patients with osteosarcoma. Cancer Chemother Pharmacol 66: 1059-1063.

Reduced time for urinary alkalinization before high-dose methotrexate with preadmission oral bicarbonate. J Oncol Pharm Pract 18:239-244

Factores de riesgo: síndrome de Down

Background
Children with Down syndrome have an increased risk of developing acute lymphoblastic leukemia and a poor tolerance of methotrexate. This latter problem is assumed to be caused by a higher cellular sensitivity of tissues in children with Down syndrome. However, whether differences in pharmacokinetics play a role is unknown.

Design and Methods
We compared methotrexate-induced toxicity and pharmacokinetics in a retrospective case-control study between patients with acute lymphoblastic leukemia who did or did not have Down syndrome. Population pharmacokinetic models were fitted to data from all individuals simultaneously, using non-linear mixed effect modeling.

Results
Overall, 468 courses of methotrexate (1-5 g/m^2) were given to 44 acute lymphoblastic leukemia patients with Down syndrome and to 87 acute lymphoblastic leukemia patients without Down syndrome. Grade 3-4 gastrointestinal toxicity was significantly more frequent in the children with Down syndrome than in those without (25.5% *versus* 3.9%; P=0.001). The occurrence of grade 3-4 gastrointestinal toxicity was not related to plasma methotrexate area under the curve. Methotrexate clearance was 5% lower in the acute lymphoblastic leukemia patients with Down syndrome (P=0.001); however, this small difference is probably clinically not relevant, because no significant differences in methotrexate plasma levels were detected at 24 and 48 hours.

Conclusions
We did not find evidence of differences in the pharmacokinetics of methotrexate between patients with and without Down syndrome which could explain the higher frequency of gastrointestinal toxicity and the greater need for methotrexate dose reductions in patients with Down syndrome. Hence, these problems are most likely explained by differential pharmacodynamic effects in the tissues between children with and without Down syndrome. Although the number of patients was limited to draw conclusions, we feel that it may be safe in children with Down syndrome to start with intermediate dosages of methotrexate (1-3 g/m^2) and monitor the patients carefully.

Table 3. Frequency of grade 3/4 toxicities in DS-ALL and non-DS-ALL patients after high-dose methotrexate therapy blocks.

Side effects	DS	Non-DS	*P* value
Including the 1st course only*			
Number of methotrexate courses	39	87	
Anemia	0/5	0/10	
Leukopenia	0/5	3/10	0.71
Neutropenia	0/4	4/7	0.37
Thrombocytopenia	0/4	0/8	
Neurological toxicity	1/38	1/76	0.60
Gastrointestinal toxicity (mucositis)	13/38	3/76	0.001
Cumulative toxicity –including courses 2-4			
Number of methotrexate courses	108	229	
Anemia	2/43	1/86	0.36
Leukopenia	10/43	9/86	0.06
Neutropenia	8/24	11/48	0.36
Thrombocytopenia	5/43	4/86	0.33
Liver toxicity (transaminases)	1/15	0/30	0.36
Neurological toxicity	1/102	1/204	0.60
Gastrointestinal toxicity (mucositis)	27/102	8/204	0.001

Methotrexate-induced side effects are not due to differences in pharmacokinetics in children with Down syndrome and acute lymphoblastic leukemia

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[1]Pediatric Oncology/Hematology, Erasmus MC–Sophia Children's Hospital, Rotterdam; [2]Department of Hospital Pharmacy and Clinical Pharmacology, Erasmus MC, Rotterdam, and [3]Dutch Childhood Oncology Group, Den Haag, the Netherlands

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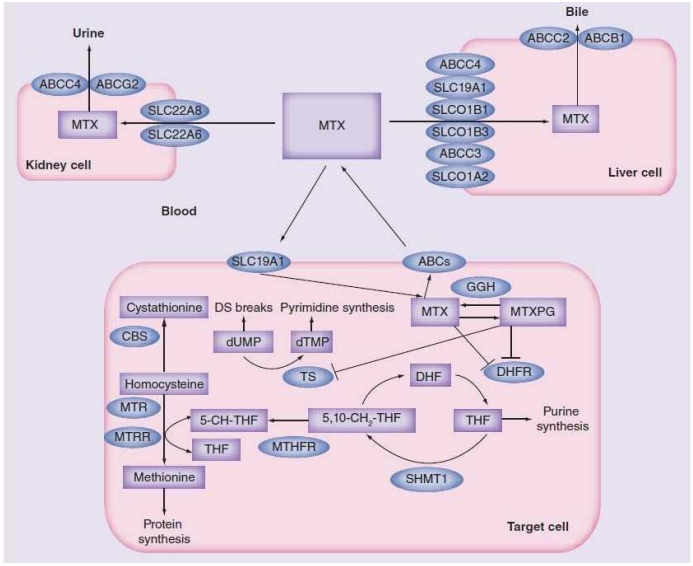
Pharmacogenetics of childhood acute lymphoblastic leukemia. **López-López E et al.** **Pharmacogenomics 2014 Jul;15(10):1383-98**

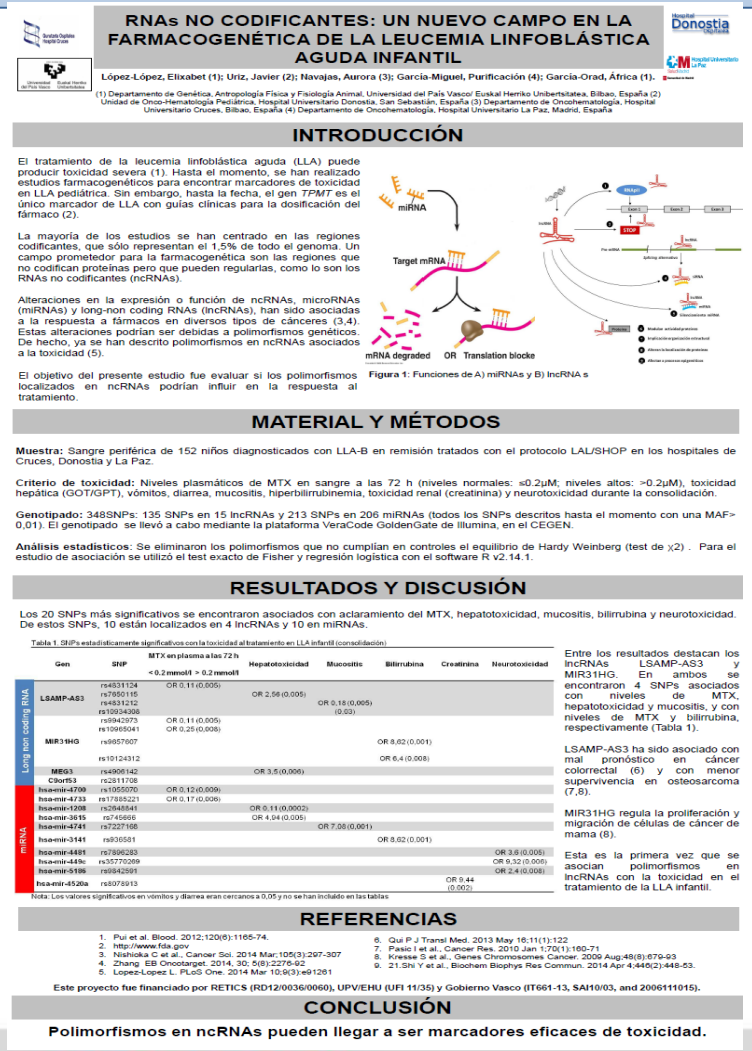
Conclusión: Algunas variantes genéticas, como las variantes C677T y A1298C en el gen MTHFR, se habían sugerido como marcadores de toxicidad y se había propuesto reducir la dosis de metotrexate en función de ellos. Según el análisis exhaustivo de la bibliografía (meta-análisis y resultados propios), no parecen ser buenos marcadores de toxicidad y no deberían ser utilizados para reducir la dosis del metotrexate en los niños con LAL.



Este mismo grupo ha identificado nuevas variantes genéticas en genes implicados en el transporte del MTX, como SLCO1B1, ABCC4 y ABCC2, que podrían ser una herramienta útil como marcadores genéticos de los individuos que podrían sufrir toxicidad.

El microRNA mir-453, implicado en la regulación de los genes que tienen la información para sintetizar las proteínas ABCC1, ABCC2 y ABCC4, encargadas de eliminar el metotrexate, podría ser un posible marcador de la toxicidad del metotrexate.

Dr. Dapena



RNAs NO CODIFICANTES: UN NUEVO CAMPO EN LA FARMACOGENÉTICA DE LA LEUCEMIA LINFOBLÁSTICA AGUDA INFANTIL

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INTRODUCCIÓN

El tratamiento de la leucemia linfoblástica aguda (LLA) puede producir toxicidad severa (1). Hasta el momento, se han realizado estudios farmacogenéticos para encontrar marcadores de toxicidad en LLA pediátrica. Sin embargo, hasta la fecha, el gen *TPMT* es el único marcador de LLA con guías clínicas para la dosificación del fármaco (2).

La mayoría de los estudios se han centrado en las regiones codificantes, que sólo representan el 1,5% de todo el genoma. Un campo prometedor para la farmacogenética son las regiones que no codifican proteínas pero que pueden regularlas, como lo son los RNAs no codificantes (ncRNAs).

Alteraciones en la expresión o función de ncRNAs, microRNAs (miRNAs) y long-non coding RNAs (lncRNAs), han sido asociadas a la respuesta a fármacos en diversos tipos de cánceres (3,4). Estas alteraciones podrían ser debidas a polimorfismos genéticos. De hecho, ya se han descrito polimorfismos en ncRNAs asociados a la toxicidad (5).

El objetivo del presente estudio fue evaluar si los polimorfismos localizados en ncRNAs podrían influir en la respuesta al tratamiento.

Figura 1: Funciones de A) miRNAs y B) lncRNA s

MATERIAL Y MÉTODOS

Muestra: Sangre periférica de 152 niños diagnosticados con LLA-B en remisión tratados con el protocolo LAL/SHOP en los hospitales de Cruces, Donostia y La Paz.

Criterio de toxicidad: Niveles plasmáticos de MTX en sangre a las 72 h (niveles normales: ≤0.2µM; niveles altos: >0.2µM), toxicidad hepática (GOT/GPT), vómitos, diarrea, mucositis, hiperbilirrubinemia, toxicidad renal (creatinina) y neurotoxicidad durante la consolidación.

Genotipado: 348SNPs: 135 SNPs en 15 lncRNAs y 213 SNPs en 206 miRNAs (todos los SNPs descritos hasta el momento con una MAF> 0,01). El genotipado se llevó a cabo mediante la plataforma VeraCode GoldenGate de Illumina, en el CEGEN.

Análisis estadísticos: Se eliminaron los polimorfismos que no cumplían en controles el equilibrio de Hardy Weinberg (test de $\chi 2$) . Para el estudio de asociación se utilizó el test exacto de Fisher y regresión logística con el software R v2.14.1.

RESULTADOS Y DISCUSIÓN

Los 20 SNPs más significativos se encontraron asociados con aclaramiento del MTX, hepatotoxicidad, mucositis, bilirrubina y neurotoxicidad. De estos SNPs, 10 están localizados en 4 lncRNAs y 10 en miRNAs.

Tabla 1. SNPs estadísticamente significativos con la toxicidad al tratamiento en LLA infantil (consolidación)

	Gen	SNP	MTX en plasma a las 72 h < 0.2 mmol/l > 0.2 mmol/l	Hepatotoxicidad	Mucositis	Bilirrubina	Creatinina	Neurotoxicidad
Long non coding RNA	LSAMP-AS3	rs4831124	OR 0,11 (0,005)					
		rs7850116		OR 2,56 (0,005)				
		rs4831212			OR 0,18 (0,005)			
		rs10934308			(0,03)			
	MIR31HG	rs9942973	OR 0,11 (0,005)					
		rs10965041	OR 0,25 (0,008)					
		rs9657607				OR 8,62 (0,001)		
		rs10124312				OR 6,4 (0,008)		
	MEG3	rs4906142		OR 3,5 (0,006)				
	C1orf53	rs2311708						
miRNA	hsa-mir-4700	rs1055070	OR 0,12 (0,009)					
	hsa-mir-4733	rs17885221	OR 0,17 (0,006)					
	hsa-mir-1208	rs2648541		OR 0,11 (0,0002)				
	hsa-mir-3615	rs745666		OR 4,94 (0,005)				
	hsa-mir-4741	rs7227168			OR 7,08 (0,001)			
	hsa-mir-3141	rs936581				OR 8,62 (0,001)		
	hsa-mir-4481	rs7896283						OR 3,6 (0,005)
	hsa-mir-449c	rs35770269						OR 9,32 (0,006)
	hsa-mir-5196	rs9842591						OR 2,4 (0,008)
	hsa-mir-4520a	rs8078913					OR 9,44 (0,002)	

Nota: Los valores significativos en vómitos y diarrea eran cercanos a 0,05 y no se han incluido en las tablas

Entre los resultados destacan los lncRNAs LSAMP-AS3 y MIR31HG. En ambos se encontraron 4 SNPs asociados con niveles de MTX, hepatotoxicidad y mucositis, y con niveles de MTX y bilirrubina, respectivamente (Tabla 1).

LSAMP-AS3 ha sido asociado con mal pronóstico en cáncer colorrectal (6) y con menor supervivencia en osteosarcoma (7,8).

MIR31HG regula la proliferación y migración de células de cáncer de mama (8).

Esta es la primera vez que se asocian polimorfismos en lncRNAs con la toxicidad en el tratamiento de la LLA infantil.

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8. Kresse S et al., Genes Chromosomes Cancer. 2009 Aug;48(8):679-93
9. 21.Shi Y et al., Biochem Biophys Res Commun. 2014 Apr 4;446(2):448-53.

Este proyecto fue financiado por RETICS (RD12/0036/0060), UPV/EHU (UFI 11/35) y Gobierno Vasco (IT661-13, SAI10/03, and 2006111015).

CONCLUSIÓN

Polimorfismos en ncRNAs pueden llegar a ser marcadores eficaces de toxicidad.

Glucarpidasa: casuística Hospital Universitario Vall d´Hebron

	Nº infusiones HDMTX	VORAXAZE®	%	Patología
2005	123	1	0,81	LAL
2006	151	0	0,0	-----
2007	124	2	1,61	LAL, OS
2008	115	0	0,0	-----
2009	122	2	1,64	LAL, LNH
2010	144	0	0,0	-----
2011	126	0	0,0	-----
2012	145	1	0,69	LAL
2013	139	3 (1 p x 2 dosis)	2,15	LAL
2014	dato no actualizado	3 (hasta junio 2014)	-----	
Total	**1189**	**9 (no 2014)**	**0,76%**	

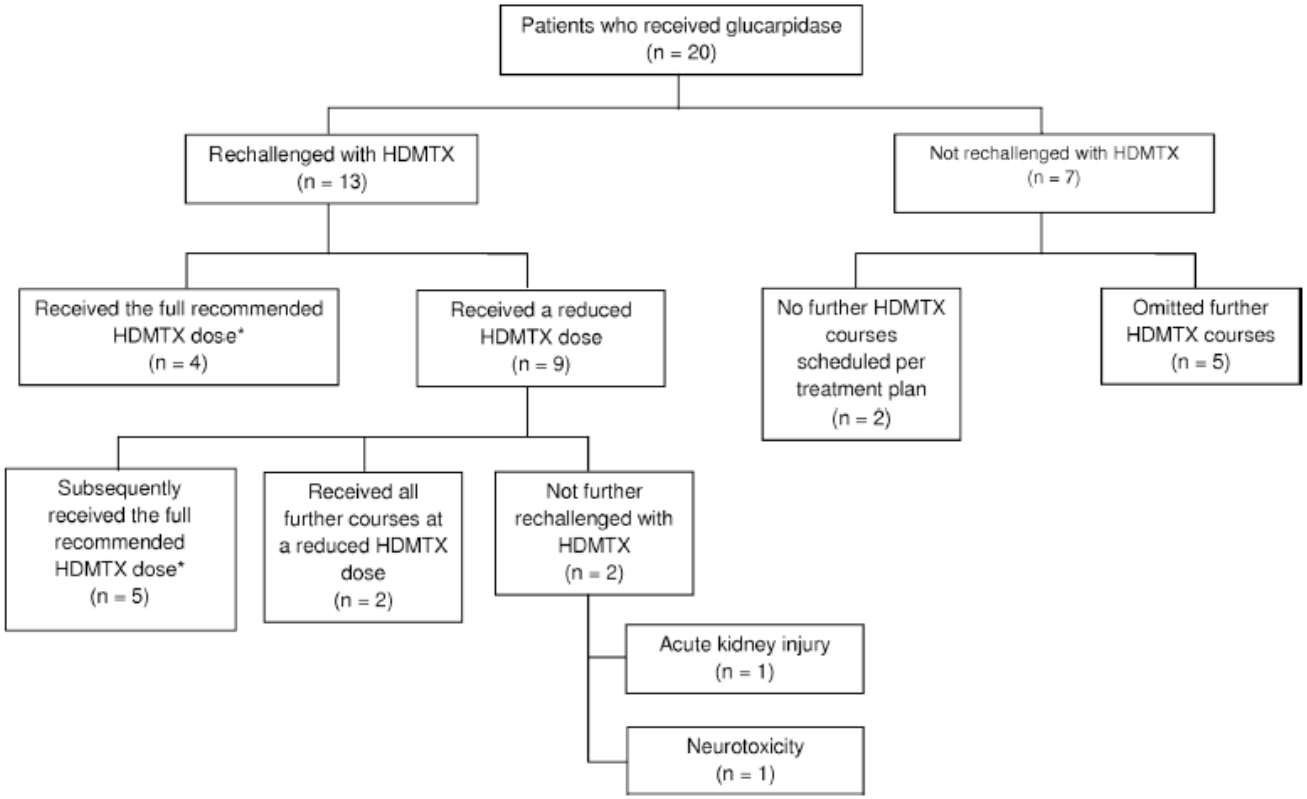
Resumption of High-dose Methotrexate after Acute Kidney Injury and Glucarpidase Use in Pediatric Oncology Patiens. Christensen A et al. Cancer 2012 September 1; 118(17): 4321-4330

Dr. Dapena

Resumption of High-dose Methotrexate after Acute Kidney Injury and Glucarpidase Use in Pediatric Oncology Patiens.

Christensen A et al. Cancer 2012 September 1; 118(17): 4321-4330

- Es posible reanudar con seguridad el tratamiento con HDMTX después del tratamiento con glucarpidasa en pacientes con toxicidad renal aguda por HDMTX



Dr. Dapena

Técnicas extracorpóreas

Efficacy of Methotrexate Removal Methods[a]

Method	No. of patients reported	No. of sessions	MTX (μM) (range)		MTX decrease (%)	Procedure duration	Postprocedure MTX rebound increase
			Preprocedure	Postprocedure			
Hemodialysis	13	23	1.0 (0.01–511)	0.8 (0.008–206)	50 (3–90)	1 Session (4 hrs to 14 days)	< 20% of postprocedure to 100% of preprocedure levels (2 patients)[b]
Hemodiafiltration	4	6	2.0 (0.19–90.0)	0.45 (0.1–2.0)	82 (44–98)	3.5 Days (1 session to 5 days)	25–43% of postprocedure levels[c]
High-flux hemodialysis	9	9	71.9 (1.45–1813.0)	42.0 (2.5–293.0)	75.5 (42.0–94.0)	4 Hrs (4–12 hrs)	≥ 50% of postprocedure levels[h]
Charcoal-hemoperfusion or hemofiltration	9	12	2.2 (0.18–328.0)	0.75 (0.01–13.5)	53 (14–95)	1 Session (3 hrs to 7 days)	20% of postprocedure (3 patients) to 90% of preprocedure levels[d]
Plasma resin perfusion	1	1	2.9	1.9	35	8 Hrs	93% of preprocedure levels (1 patient)[e]
Peritoneal dialysis	2	2	1.77 (0.53–3.0)	Minimal decrease	Minimal decrease	4.5 Days (2–7 days)	—
Exchange transfusion or plasma exchange	10	22	3.8 (0.12–32.0)	2.3 (0.12–37.0)	26 (0–72)	1 Session (5 hrs to 1 session)	20% of postprocedure levels (3 patients)[f]
Charcoal-hemoperfusion/ hemofiltration and hemodialysis	8	10	12.7 (0.9–390.0)	2.2 (0.2–14.0)	78 (38–98)	1.0 Day (6 hrs to 6.25 days)	10% and 56–221% (1 patient each) of postprocedure levels[g]

Dr. Dapena

HDMTX en tumores sólidos y hematológicos: Intoxicación.

Dr. Francisco José Bautista.

- **Si un paciente se intoxica en un ciclo: ¿debo reducir la dosis en los ciclos siguientes?**
- **Si necesito forzar diuresis: ¿cuál es el diurético más adecuado?**
- **Si no consigo alcalinizar la orina: ¿es la acetazolamida una buena opción?**

¿Si un paciente se intoxica en un ciclo debo reducir la dosis en los ciclos siguientes en OS?

Dr. Bautista

Depende:

-Del tipo de toxicidad

-Del grado de toxicidad

-De la duración de la toxicidad

		OS 2006 (Francia)	SEHOP OS 2010 (España)	EURAMOS
TOXICIDAD	**GRADO**	**MODIFICACIONES**		
Hematológica	**- Neutropenia G4 - Trombopenia G3**	**----------**	**----------**	**- Retrasar 1 semana el MTX**
Digestiva	**- Mucositis G3-4 - Diarrea G3-4**	**- Adelantar las dosis de AF en los ciclos siguientes**	**- Considerar aumentar rescates con AF u omitir el ciclo MTX**	**- Considerar aumentar rescates con AF u omitir el ciclo MTX**
Renal	**-FG <70-60ml/min -Cr >1,5 x ULN**	**- Retrasar hasta la recuperación - Omitir si no se recupera y pasar al siguiente ciclo**	**- Retrasar hasta la recuperación - Omitir si no se recupera y pasar al siguiente ciclo**	**- Retrasar hasta la recuperación - Omitir si no se recupera y pasar al siguiente ciclo**
Hepática	**- Hipertrans G3-4 - Hiper Bili >1,25-1,5 x ULN**	**- Si Hipertrans G3-4 > 2 Semanas reducir MTX a 8g - Si Hiper B >3 semanas, suspender MTX**	**- Retrasar 1 semana el MTX - Si Hipertrans G3-4 > 3 Semanas suspender MTX**	**- Retrasar 1 semana el MTX - Si Hipertrans G3-4 > 3 Semanas suspender MTX**
Neurológica	**-Neurotox G3 transitoria -Neurotox G2 >48h o G4**	**----------**	**-Reanudar MTX con vigilancia -Suspender MTX**	**----------**

¿Un retraso en un ciclo de MTX, se considera un factor pronóstico negativo en OS ?

Dr. Bautista

-Concepto de dosis intensidad en oncología pediátrica todavía no bien establecido

EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment†

Med Oncol. 2014 May;31(5):936. doi: 10.1007/s12032-014-0936-1. Epub 2014 Apr 10.

Is it important to maintain high-dose intensity chemotherapy in the treatment of adults with osteosarcoma?

Kushnir I[1], Kolander Y, Bickels J, Gortzak Y, Flusser G, Issakov J, Merimsky O.

Si necesito forzar diuresis, ¿cuál es el diurético más adecuado?

Dr. Bautista

En caso de diuresis **inferior a 2l/m²/día**, se puede utilizar la **furosemida** para favorecer la diuresis. En cualquier caso, es imperativo descartar otras causas como perdidas digestivas, que obliguen a adaptar el tratamiento antiemético y consecuentemente a aumentar la hidratación.

Si no consigo alcalinizar la orina, ¿es la acetazolamida una buena opción?

Cancer Chemother Pharmacol. 1991;28(2):150-1.

Acetazolamide for alkalinisation of urine in patients receiving high-dose methotrexate.

Shamash J[1], Earl H, Souhami R.

HDMTX en tumores sólidos y hematológicos: Intoxicación.

Dra. M. Dolores Aumente.

- En caso de intoxicación grave por MTX:

¿Cuáles son las medidas a adoptar?

¿Cuáles son las medidas a adoptar en caso de intoxicación severa?

Medidas correctoras

- ✓ **Incrementar la dosis de Ac folínico**
- ✓ **Favorecer la eliminación de MTX**
  - ✓ **Diuresis forzada alcalina (diuresis de 0.5-10ml/min)** — **90%**

    Aumentar hidratación 4.5L/m²/día

    Mantener ph ≥ 7 hasta MTX ≤ 0,2 μM
  - ✓ **Interrupción del ciclo enterohepático** — **10-30%**

    Carbón activo: *50g+25g/4-6h (niños 1g/kg max:50g)*

    Colestiramina: *4g/6h (niños 240mg/kg/día en 3-4 dosis)*
  - ✓ **Hemodiálisis de alto flujo o TRRC (HFVVC o HDFVVC)** — **75% (42-94)**
- ✓ **Inactivar el metotrexate: Carboxipeptidasa** — **97%(73-99)**

  (Glucarpidase o voraxaze)

Dra. Aumente

¿Cuál es la concentración límite que no se puede rescatar únicamente con LV?

Pinedo HM et al. Cancer Research 1976; 36:4418-4424

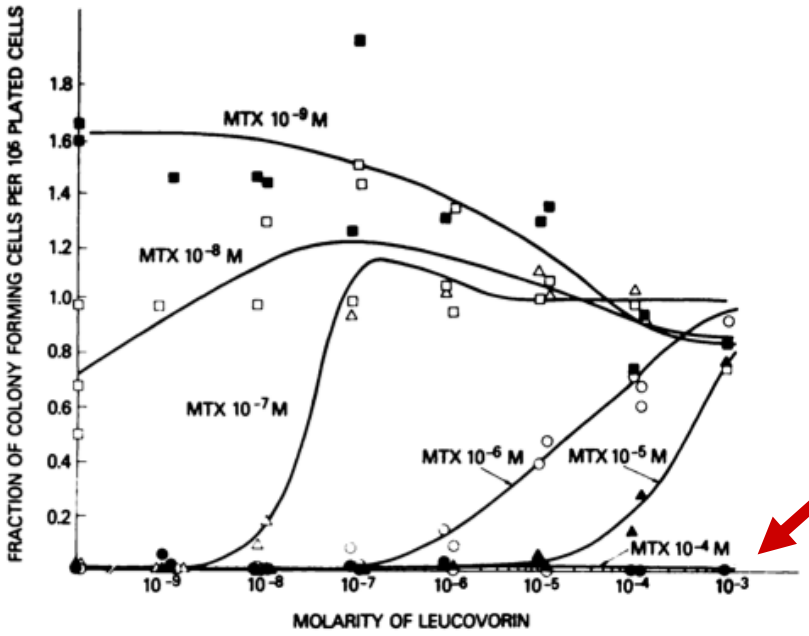


Chart 5. The effects of leucovorin on MTX cytotoxicity at different concentrations of the drug. ■, MTX 10^{-9} M; □, MTX 10^{-8} M; △, MTX 10^{-7} M; ○, MTX 10^{-6} M; ▲, MTX 10^{-5} M; ●, MTX 10^{-4} M.

Effects of Leucovorin. The inhibitory effects of MTX in concentrations of 10^{-7} M or less could be effectively reversed by adding equimolar concentrations of leucovorin to the media (Chart 5).

However, it was more difficult to reverse the inhibiting effects of higher concentrations of MTX; cells cultured in 10^{-6} M MTX were rescued by 10^{-4} M leucovorin, and cells cultured in 10^{-5} M MTX were rescued by 10^{-3} M leucovorin. We were unable to rescue cells cultured in 10^{-4} M MTX by 10^{-3} M leucovorin. Addition of still higher concentrations of leucovorin resulted in the formation of a precipitate in the medium. The slight stimulatory effects of 10^{-9} M MTX were

C_{42h}=50-100 µM → 500mg/m²/3h

>100 µM???

[MTX sérica] ≥42h desde inicio infusión de MTX	[THF] deseada	Dosis de LV
20-50µM	200-500µM	500mg/m² IV/6h
10-20µM	100-200µM	200mg/m² IV/6h
5-10µM	50-100µM	100mg/m² IV/6h
1-5µM	5-10µM	30mg/m² IV o vo/6h
0.6-1µM	0.6-1µM	15mg/m² IV o vo/6h
0.1-0.5µM	0.1-0.5µM	15mg/m² vo/12h
0.05-0.1µM	0.05-0.1µM	5-10mg/m² vo/12h

Evans WE, Shentag JJ, Jusko WJ. Applied pharmacokinetics. Principles of therapeutic Drug Monitoring. 3ª ed. Vancouver: Applied Therapeutic Inc. 1992.

Dra. Aumente

Resumption of High-dose Methotrexate after Acute Kidney Injury and Glucarpidase Use in Pediatric Oncology Patients

Anthony M. Christensen, Pharm.D.[1], Jennifer L. Pauley, Pharm.D.[1,2], Alejandro R. Molinelli, Ph.D.[3], John C. Panetta, Ph.D.[2,3], Deborah A. Ward, Pharm.D.[1,2], Clinton F. Stewart, Pharm.D.[2,3], James M. Hoffman, Pharm.D., M.S.[2,3], Scott C. Howard, M.D., M.S.[4,5], Ching-Hon Pui, M.D.[4,5], Alberto S. Pappo, M.D.[4,5], Mary V. Relling, Pharm.D.[2,3,4], and Kristine R. Crews, Pharm.D.[2,3,*]

Cancer. 2012 September 1; 118(17): 4321–4330. doi:10.1002/cncr.27378.

Characteristics of 20 patients at the time they received glucarpidase for delayed methotrexate clearance out of 1,141 patients who received HDMTX.

5g/m² en 24h

	All Patients	Osteosarcoma	ALL	Other
Percent (No.) of patients who received glucarpidase	1.8% (20 of 1,141)	8% (6 of 75)	1.3% (10 of 741)	1.2% (4 of 325)
Plasma MTX concentrations by TDx				
20 – 24 hrs post-MTX (M)			44-48h	
Median	138.0	353.1	114.42	99.2
Range	29.2 – 462.9	158.8 – 462.9	65.7 – 222.1	29.2 – 258
Time to 1st glucarpidase dose (hrs)				
Median	45.9	30	47.8	45.9
Range	26.3 – 95	28 – 46.5	26.3 – 95	28.8 – 48
Prior to glucarpidase (M)				
Median	29.1	267.3	18.1	54.6
Range	1.3 – 590.6	32.2 – 590.6	1.3 – 222.1	16.5 – 239.8
Time to complete MTX excretion (hrs)				
Median	355	407	344	415
Range	244 – 763	295 – 763.2	245 – 497	259.2 – 540

Si T_{inf}=24h → C_{36h}>100 µM

HIGHLIGHT

by Brigitte C. Widemann, MD*

Pediatr Blood Cancer 2015;62:1512–1513

Practical Considerations for the Administration of Glucarpidase in High-Dose Methotrexate (HDMTX) Induced Renal Dysfunction

Limit the administration of gucarpidase to patients with plasma MTX concentrations ≥10mM at 42–48 hr after start of the MTX infusion.

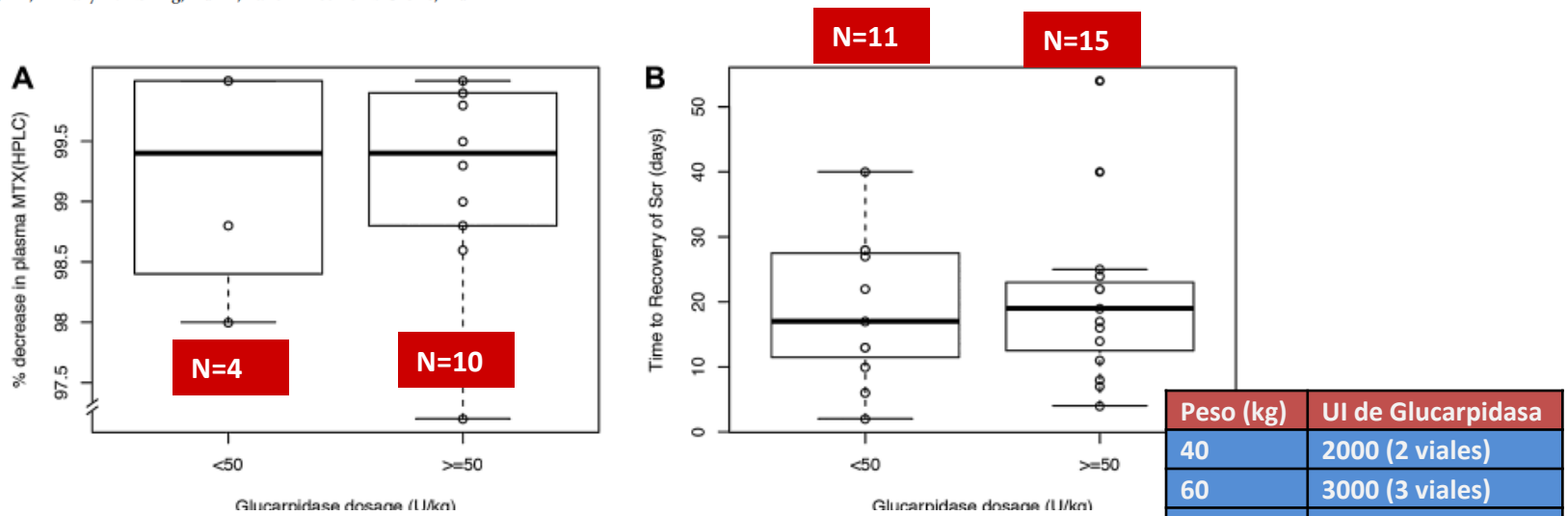
Dra. Aumente

Si no dispongo de suficiente glucarpidasa ¿la utilización de dosis menores puede ser eficaz?

Pediatr Blood Cancer 2015;62:1518–1522

Comparable Efficacy With Varying Dosages of Glucarpidase in Pediatric Oncology Patients

Jeffrey R. Scott, PharmD,[1]* Yinmei Zhou, MS,[2] Cheng Cheng, PhD,[2] Deborah A. Ward, PharmD,[1] Hope D. Swanson, PharmD,[1] Alejandro R. Molinelli, PhD,[1] Clinton F. Stewart, PharmD,[1] Fariba Navid, MD,[3,4] Sima Jeha, MD,[3]* Mary V. Relling, PharmD,[1] and Kristine R. Crews, PharmD[1]



Peso (kg)	UI de Glucarpidasa
40	2000 (2 viales)
60	3000 (3 viales)
80	4000 (4 viales)
100	5000 (5 viales)

TABLE I. Patient Characteristics of 26 Patients at the Time They Received Glucarpidase for Delayed Methotrexate Clearance

Characteristic	All patients (n=26)	OS (n=10)	ALL (n=12)	Other (n=4)
Methotrexate dosage, g/m^2 Median Range	7.4 2.5–12.4	12.0 11.5–12.4	4.6 2.5–8	6.1 3.3–8
Methotrexate infusion time, hr Median Range	11 4–24.1	4 4–6	24 4–24.1	11 4–20
Glucarpidase dosage, units/kg Median Range	50.8 13.0–90.1	51.6 15.0–65.6	50.8 13.0–90.1	39.3 21.0–65.0
Pre-glucarpidase MTX concentration (TDx), μmol Median Range	38.6 1.31–590.6	154.3 32.2–590.6	15.7 1.31–222.1	54.6 16.5–239.8
Post-glucarpidase MTX concentration (TDx), μmol Median Range	5.6 0.35–82.8	8.8 0.7–82.8	4 0.35–36.9	6.8 1–26.8
Post-glucarpidase MTX concentration (HPLC), μmol Median Range	0.75 <0.15–5	1.4 0.3–5	0.15 <0.15–3.6	

Dosis de glucarpidasa=2000 UI (2 viales) ⇒ ↓dosis en >40kg

Dra. Aumente

Si no dispongo de HPLC ¿qué puedo hacer?

Resumption of High-dose Methotrexate after Acute Kidney Injury and Glucarpidase Use in Pediatric Oncology Patients

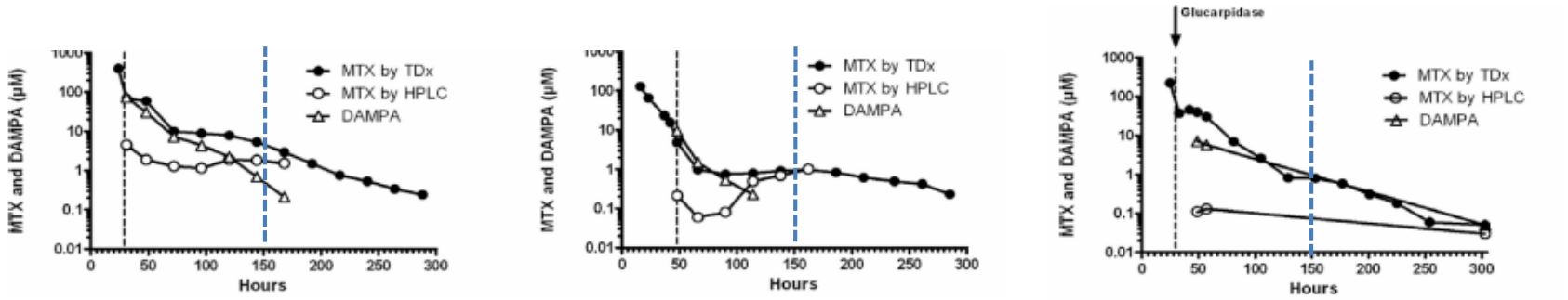
Anthony M. Christensen, Pharm.D.[1], Jennifer L. Pauley, Pharm.D.[1,2], Alejandro R. Molinelli, Ph.D.[3], John C. Panetta, Ph.D.[2,3], Deborah A. Ward, Pharm.D.[1,2], Clinton F. Stewart, Pharm.D.[2,3], James M. Hoffman, Pharm.D., M.S.[2,3], Scott C. Howard, M.D., M.S.[4,5], Ching-Hon Pui, M.D.[4,5], Alberto S. Pappo, M.D.[4,5], Mary V. Relling, Pharm.D.[2,3,4], and Kristine R. Crews, Pharm.D.[2,3,*]

Cancer. 2012 September 1; 118(17): 4321–4330. doi:10.1002/cncr.27378.

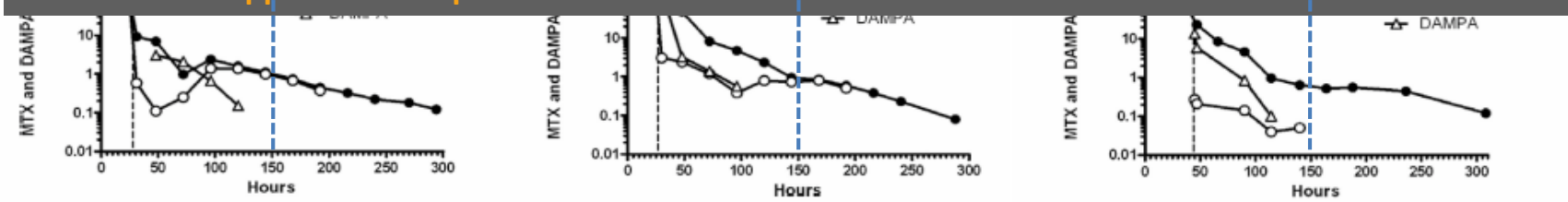
$CPDG_2$ y DAMPA muestran reactividad cruzada con el MTX determinado por inmunoensayos como el FPIA

DAMPA : $T_{1/2}$=9-12h —26%→ **~~[DAMPA]~~<1µM a los 4 días**

$CPDG_2$: $T_{1/2}$=9 h —59%→ **[$CPDG_2$] se elimina en 8 horas**



However, in the absence of an HPLC assay, commercial methods can be used to guide the duration of leucovorin rescue because DAMPA metabolite levels become insignificant as the plasma methotrexate concentration approaches 0.1 µM



Dra. Aumente

Efficacy of Glucarpidase (Carboxypeptidase G2) in Patients with Acute Kidney Injury After High-Dose Methotrexate Therapy

Brigitte C. Widemann,[1] Stefan Schwartz,[2] Nalini Jayaprakash,[1] Robbin Christensen,[3] Ching-Hon Pui,[3] Nikhil Chauhan,[4] Claire Daugherty,[4] Thomas R. King,[4*] Janet E. Rush,[4] and Scott C. Howard[3]
[1]National Cancer Institute, Bethesda, Maryland; [2]Charité Universitätsmedizin Berlin, Berlin, Germany; [3]St. Jude Children's Research Hospital, Memphis, Tennessee; [4]BTG International Inc., West Conshohocken, Pennsylvania

(Pharmacotherapy 2014;34(5):427–439)

Resumption of High-dose Methotrexate after Acute Kidney Injury and Glucarpidase Use in Pediatric Oncology Patients

Anthony M. Christensen, Pharm.D.[1], Jennifer L. Pauley, Pharm.D.[1,2], Alejandro R. Molinelli, Ph.D.[3], John C. Panetta, Ph.D.[2,3], Deborah A. Ward, Pharm.D.[1,2], Clinton F. Stewart, Pharm.D.[2,3], James M. Hoffman, Pharm.D., M.S.[2,3], Scott C. Howard, M.D., M.S.[4,5], Ching-Hon Pui, M.D.[4,5], Alberto S. Pappo, M.D.[4,5], Mary V. Relling, Pharm.D.[2,3,4], and Kristine R. Crews, Pharm.D.[2,3,*]

Cancer. 2012 September 1; 118(17): 4321–4330.

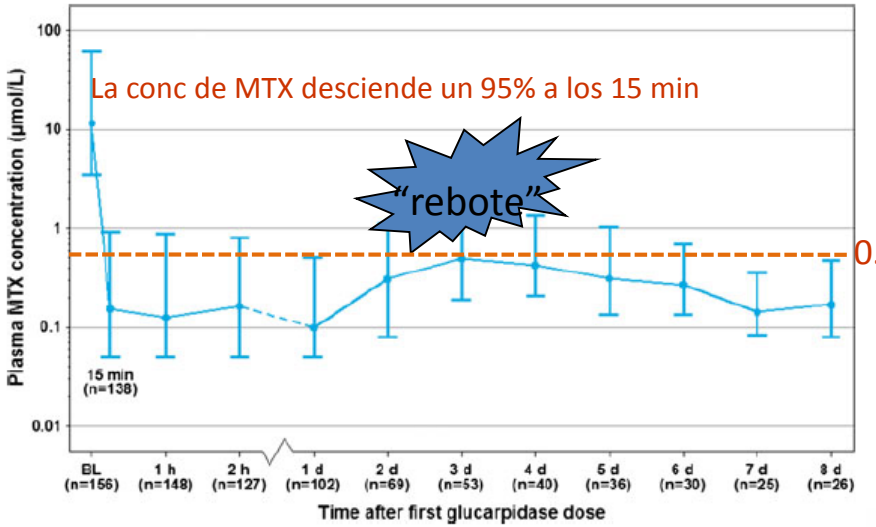
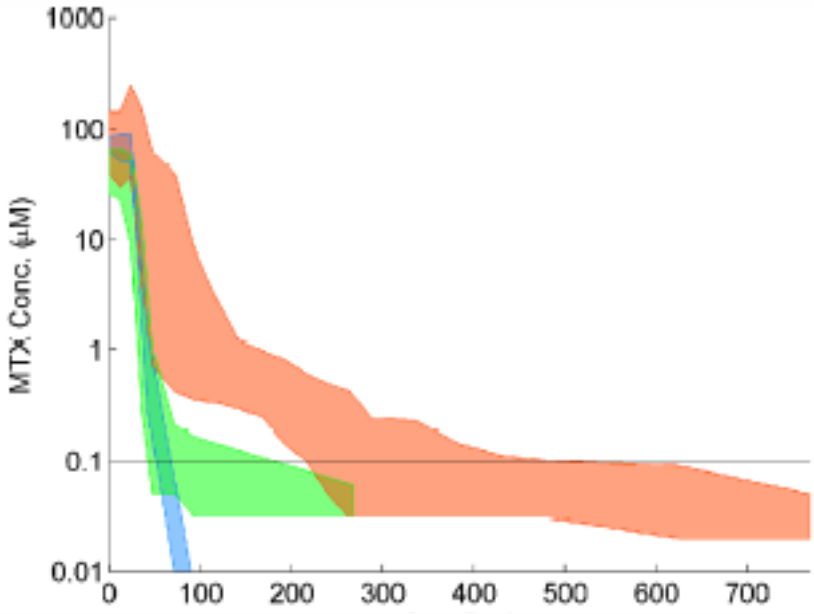


Figure 1. Methotrexate (MTX) concentrations (median [25th and 75th percentiles]) after treatment with glucarpidase in 1 of 169 efficacy-evaluable patients who had preglucarpidase (baseline [BL]) and postglucarpidase MTX measurements by hig performance liquid chromatography.



	All Patients	Osteosarcoma	ALL	Other
Percent (No.) of patients who received glucarpidase	1.8% (20 of 1,141)	8% (6 of 75)	1.3% (10 of 741)	1.2% (4 of 325)
Time to complete MTX excretion (hrs)				
Median	355	407	344	415
Range	244 – 763	295 – 763.2	245 – 497	259.2 – 540

10-31 días

Dra. Aumente

¿Puede evitar la glucarpidasa la muerte por intoxicación con MTX?

Glucarpidase for the management of elevated methotrexate levels in patients with impaired renal function

MARIANA FERMIANO, JASON BERGSBAKEN, AND JILL M. KOLESAR

Am J Health-Syst Pharm. 2014; 71:793-8

Table 1.
Summary Data on Glucarpidase Efficacy and Safety in Clinical Trials

Variable	Buchen et al.[14] (2005) *n* = 65	Schwartz et al.[4] (2007) *n* = 43	Widemann et al.[8] (2010) *n* = 100	Christensen et al.[9] (2012) *n* = 20
Median (range) age, yr	15.4 (0.9–71.8)	54 (18–78)	17.4 (0.3–82.0)	12.1 (4.1–20.4)
Median (range) baseline methotrexate concentration, µM/L	11.93 (0.52–901.0)	10.5 (1.0–1187.0)	28.20 (0.37–849.0)	29.1 (1.3–590.6)
Median (range) time to glucarpidase infusion, hr	52 (25–178)	56 (27–176)	96 (22–294)	45.9 (26.3–95.0)
Mean reduction in serum methotrexate at 15 min, %	88.0	97.0	98.7	99.6
No. patients who received concurrent dialysis-related therapy	6	5	27	1
No. patients who received more than 1 glucarpidase dose	9	3	6	4
No. (%) deaths attributed to high-dose methotrexate	3 (4.6)	10 (23.0)	6 (6.0)	0

Dra. Aumente

Glucarpidase, Leucovorin, and Thymidine for High-Dose Methotrexate-Induced Renal Dysfunction: Clinical and Pharmacologic Factors Affecting Outcome

Brigitte C. Widemann, Frank M. Balis, AeRang Kim, Matthew Boron, Nalini Jayaprakash, Aiman Shalabi, Michelle O'Brien, Michelle Eby, Diane E. Cole, Robert F. Murphy, Elizabeth Fox, Percy Ivy, and Peter C. Adamson

$CPDG_2=C_{42h}$>10µM

Inicio= 96h (22-294h)

MTX pre=28.2µM (0.37-849)

Factores de riesgo de toxicidad:

- **Glucarpidasa>96 h**
- **Rescate inapropiado**
- **Toxidad grado IV previa**

Fallecen 12 pacientes:

- **6 por toxicidad por MTX**
- **6 por progresion de la enfermedad**

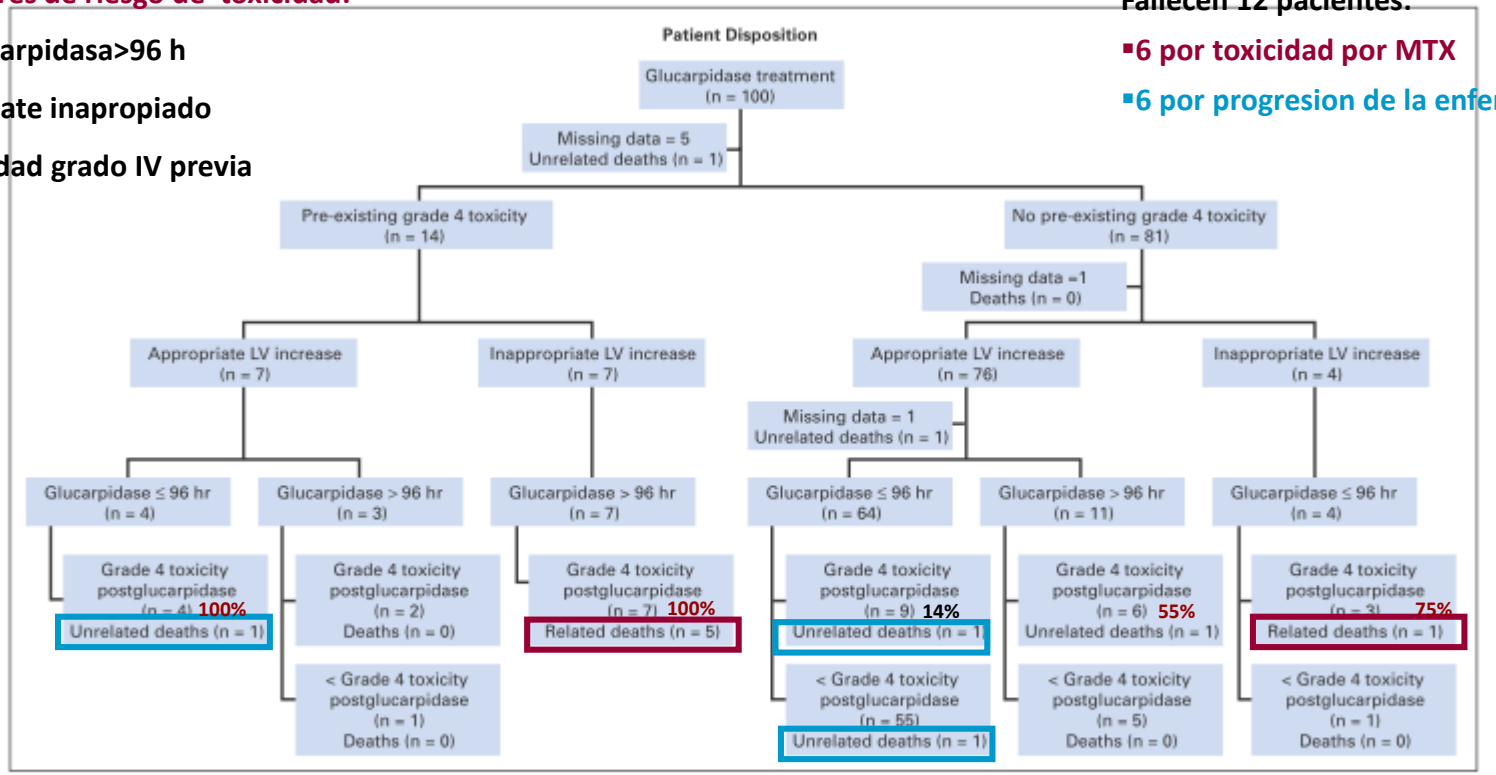


Fig 1. Disposition of 100 patients who received glucarpidase, indicating pre-existence or absence of grade 4 toxicity before administration of glucarpidase; appropriate or inappropriate increase in leucovorin (LV) rescue within 3 days after the start of high-dose methotrexate (HDMTX); timing of administration of glucarpidase at ≤ 96 hours or more than 96 hours after starting HDMTX; presence of grade 4 toxicity after the administration of glucarpidase; and death directly attributed or not directly attributed to MTX toxicity.

Dra. Aumente

HDMTX en tumores sólidos y hematológicos: Intoxicación.

Dra. Azucena Aldaz.

- **Prevención y manejo toxicidad de la toxicidad por MTX**

Relación Concentración-Toxicidad

Pauta de MTX	Tiempo desde el inicio de la infusión (h)	Concentración de riesgo
1-2 g/m2 en bolus IV y 800 mg/m2 en infusión de 24 h	42	>0,5 µmol/L
1,5-2 g/m2 en infusión de 1 h y 1,3 g/m2 en 23 h	42	>1 µmol/L
12 g/m2 en infusión de 4 h	24 28 48 72	>10 µmol/L >5 µmol/L >1 µmol/L >0,2 µmol/L

Concentraciones de alto riesgo con distintas pautas empleados en el St Jude (Memphis,Tenessee)

Dra Aldaz

Concentración de MTX/tiempo asociados a riesgo de toxicidad

Referencia	Pauta de MTX	Concentración de riesgo de MTX (μmol/L)
Tattersall 1975	1-15 g/m2 en bolus	C48h>0,5
Stoller 1977	50-250 mg/kg en 6 h	C48h>0,9
Skarin 1977ª	1-7,5 g/m2 en 0,5 h	C24h>5
Nirenberg 1977	8 g/m2 en 4 h	C24h>10 C48h>1 C72h>0,1
Isacoff 1977	50-200 mg/kg en 4 h	C24h>10 C48h>0,5
Evans 1979	725-15000 mg/m2 en 6 h	C24h>5 T1/2α>3,5 h
Frei 1980	3-7,5 g/m2 en 0,3 h	C24h>5
Bertino 1981	> 500 mg/m2 en 1-42 h	C24h>1,5

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Rosen 1982	8-12 g/m2 en 4 h	C24h>20 C48h>2 C72h>0,2
Jaffé 1983b	12,5 g/m2 en 6 h	C72h>0,3
Jaffé 1985	1,5-7,5 g/m2 en 6 h	C48h>0,3
Crom 1985	12 g/m2 en 4 h	C20h>10 C24h>5 C44h>1 T1/2α>3,5 h
Parker 1986	500 mg/m2 en 24 h	C24h>4,8
Jaffé 1987	12,5 g/m2 en 6 h	C24h>300 C48h>30 C72h>0,3
Christensen 1988	500 mg/m2 en bolus y 1500 mg/m2 en 2 h	C44h>0,8

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Raude 1988		T1/2α>3,1 h C24h>6,3 C48h>0,77 C72h>0,33
Reggev 1988	24-33 g/m2	C24h>500 C48h>10 C72h>1
Aldaz 1989	6-12 g/m2 en 4 h	C24h>3,5 y T1/2α>3,5 h C48h>0,35 y T1/2β>12,5 h
Alós Almiñana 1991	13,7 + 1 g en perfusión de 4 ó 6 h	Criterio A: t1/2 12 h>3 h Criterio B: t1/2 24 h>3,5 h
Climente 1994	8-12 g /m2 en 6 h	t1/2 12 h>2,5 h

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Prevention of high-dose-methotrexate neurotoxicity by adequate folinic acid rescue is possible even after central nervous system irradiation

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Medical Hypotheses (2007) 68, 1147–1153

Table 1 Dose of folinic acid needed to prevent neurotoxicity

Methotrexate	Folinic acid	Outcome	Folinic acid (mg/m^2)	Outcome
50–10 mg/kg	0	Neurotoxicity [22]	10	No neurotoxicity [23,6]
1 g/m^2	25 mg/m^2	Neurotoxicity [1]	45	No neurotoxicity [24]
6–8 g/m^2	120 mg	Neurotoxicity [25]	180	No neurotoxicity [13]
20 g/m^2			760	No neurotoxicity [26]

neurotoxicity [24]. Treatment with 6–8 g/m^2 MTX followed by 120 mg/m^2 folinic acid caused neurotoxicity [25], whereas 8 g/m^2 MTX followed by 180 mg/m^2 folinic acid did not [15]. Likewise, a dose of folinic acid can reduce efficacy. However, the actual dose of folinic acid needed to neutralize the effect of high-dose MTX is enormous. We described a patient with osteogenic sarcoma treated with 27.5 g (15 g/m^2) MTX who was ''over-rescued'' with 1275 mg folinic acid, leading to tumor regrowth [41]. We could find no other report of ''over-rescue'' by folinic acid after high-dose MTX.

Understanding and Managing Methotrexate Nephrotoxicity

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The Oncologist 2006;11:694–703

Table 1. Plasma methotrexate concentrations indicating a high risk for the development of methotrexate (MTX)-associated toxicities

Dosage regimen		No. of patients/ MTX cycles	Defined toxic MTX concentration	No. of toxic concentration/ toxicity	Study
Methotrexate	**Leucovorin**				
1–15 g/m^2 over 20 hrs or 1 g/m^2 as bolus	40 mg/m^2 at hr 24, then 25 mg/m^2 q6h × 12 doses	52/?	>≈0.9 μM at 48 hrs >≈0.5 μM at 72 hrs	?	Tattersall et al. [75]
2 g/m^2 as bolus or over 20 hrs	40 mg/m^2 at hr 24, then 256 mg/m^2 q6h × 12	?/40	>0.1 μM at 72 hrs	7/8	Pitman et al. [76]
50–250 mg/kg over 6 hrs	15 mg/m^2 q6h × 8, start 2 hrs post-MTX (augmented for some pts with MTX >0.9 μM at 48 hrs)	78 /395	>0.9 μM at 48 hrs	12/5	Stoller et al. [12]
8 g/m^2 over 4 hrs	9–15 mg q6h × 12 starting 2 hrs post-MTX	?	>10 μM at 24 hrs >1 μM at 48 hrs >0.1 μM at 72 hrs	74/24 68/25 96/20	Niren-berg et al. [77]
50–300 mg/kg over 4 hrs	40 mg/m^2 4 hrs post-MTX then 15 mg q6h × 11 (augmented for all pts with MTX >10 μM at 24 hrs)	134/496	>10 μM at 24 hrs	83/12	Isacoff et al. [78]
725–15,000 mg/ m^2 over 6 hrs	5–90 mg/m^2 q3h × 8 starting 3 hrs post-MTX then 12 mg/m^2 q6h × 8 (augmented for all pts with 24-hr MTX >5 μM)	?/114	>5 μM at 24 hrs and MTX $t_{1/2}$ >3.5 hrs	5/1	Evans et al. [79]

Abbreviations: hr, hour; pts, patients; q3h, every 3 hours; q6h, every 6 hours; $t_{1/2}$, half-life.

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Toxicidad gastrointestinal

Vómitos **POST** **(p=0,030)** **RO = 1,12 (1,011-1,24)**

Mucositis **Retraso** **(p<0,00001)** **RO = 5,76 (1,32-23,59)**

Toxicidad renal

Crs y C_{24h} (p=0,00064) **RO_{C24h}= 1,43 (1,10-1,86)**

C_{24h}>3,5µM **(p=0,018)**

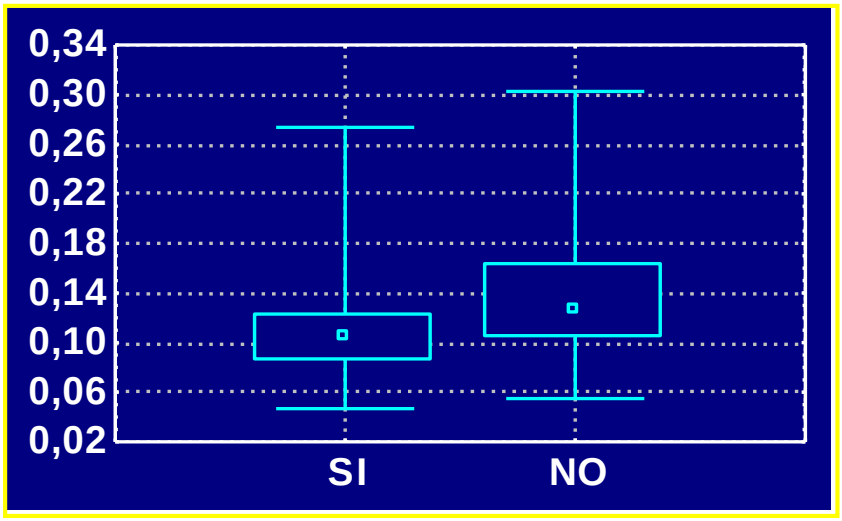
RO = 2,09

R= 0,66381692 R^2= 0,44065291 R^2 ajustada= 0,43184429
F(2,127)=50,025 p<0,00000 Error estándar estimado: 18,231

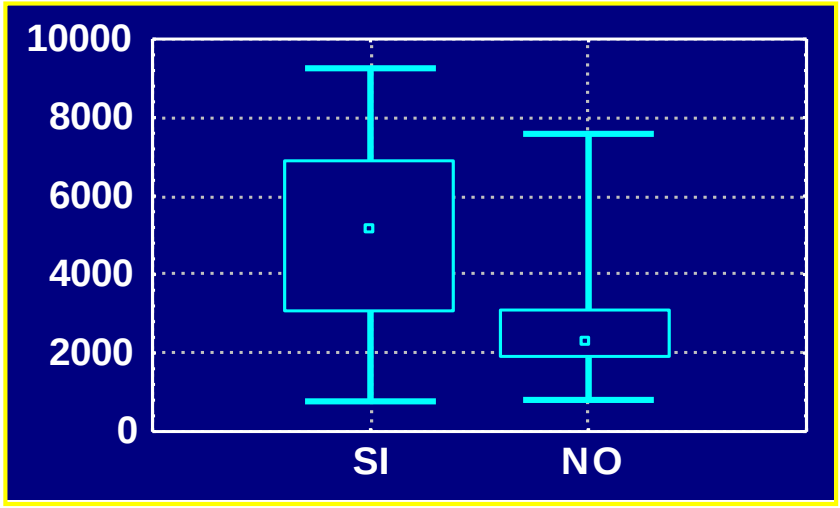
	BETA	Error est. de Beta	B	Error est. de B	t(127)	p-level
Intercpt			38,9138	5,949276	6,54094	0,000000
C24h	0,741747	0,074242	7,1525	0,715904	9,99091	0,000000
Crs	-0,364485	0,074242	-45,8182	9,332752	-4,90940	0,000003

Análisis de los ciclos con retraso en la eliminación

CL en L/h/kg



AUC en µM



Regresión logística

C. Postinfusión (p<0,0000001)

$$RO_{100\ \mu M} = 1{,}50\ (1{,}31\text{-}1{,}72)$$

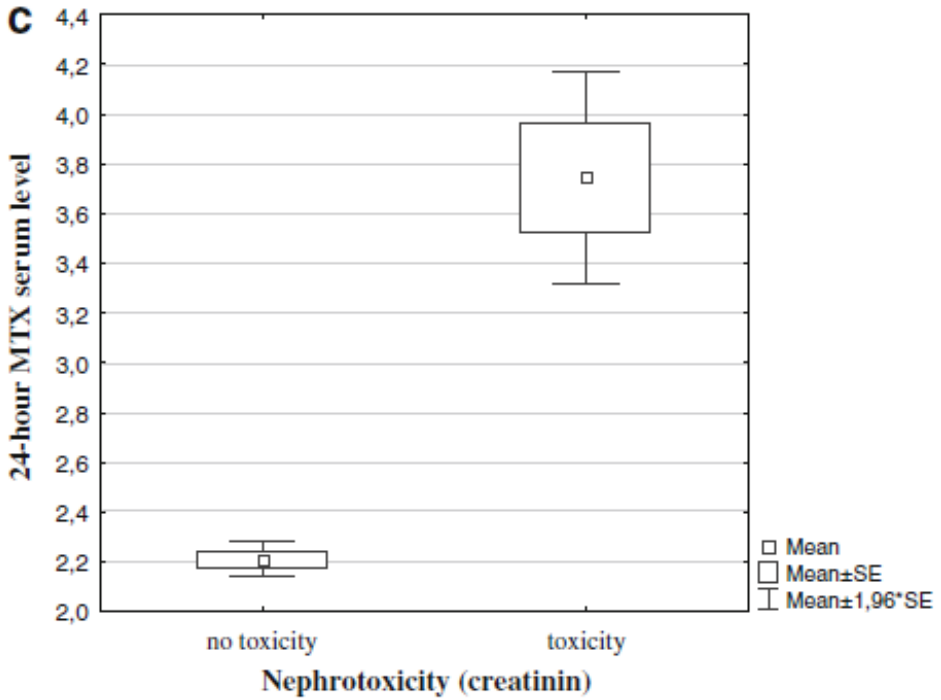
Dra Aldaz

Clinical relations of methotrexate pharmacokinetics in the treatment for pediatric osteosarcoma

Marta Hegyi · Ágnes Gulácsi · Edit Cságoly · Katalin Csordás · Olivér T. Eipel · Dániel J. Erdélyi · Judit Müller · Karolina Nemes · Orsolya Lautner-Csorba · Gábor T. Kovács

All patients were administered 12 g/m^2 HD-MTX over 6 h with leucovorin rescue. Patients received oral and intravenous hydration fluids (3 l/m^2/day) the day before, during and 48 h after HD-MTX therapy and sodium bicarbonate for urine alkalinization. Leucovorin rescue was started at 30 h after the initiation of the HD-MTX infusion at a dose of 15 mg/m^2 every 6 h for a total of 5 doses.

MTX serum levels were measured at the end of 6-h infusion (peak level), and 24, 36 and 48 h after the initiation of the infusion by high pressure liquid chromatography (HPLC) method. AUC_{0-48h} (area under the concentration–time curve 0–48 h) was calculated according to the trape-



Dra Aldaz

EURAMOS-1

Guidance for use of Carboxypeptidase-G2 during delayed methotrexate excretion

Carboxypeptidase-G2 can be used to treat patients with methotrexate-induced renal dysfunction and delayed methotrexate excretion. It results in significantly diminished serum methotrexate levels usually within minutes. Use of carboxypeptidase should be considered if:

- Serum methotrexate concentration ≥10micromol/L 48 hours after methotrexate administration
- Rise in creatinine of 100% or more within 24 hours of methotrexate.

Carboxypeptidase-G2 should be initiated following consultant request only.

Dra Aldaz